A “Methyl Extension” Strategy for Natural Product Linker Site Validation and its Application to Dictyostatin

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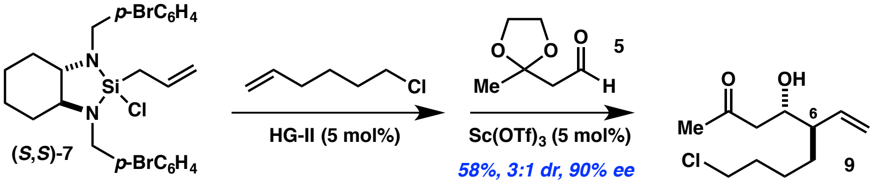
Supporting Information

General Information. All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring unless otherwise indicated. Degassed solvents were purified by passage through an activated alumina column. Thin-layer chromatography was carried out on glass backed silica gel TLC plates (250 mm) from Silicycle. Visualization was accomplished with UV light (254 nm), followed by heating after staining the plate with phosphomolybdic acid or ceric ammonium molybdate solution. Optical rotations were recorded on a Jasco DIP-1000 digital polarimeter. Infrared spectra were recorded on a Perkin-Elmer Spectrum Two (Diamond ATR) IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AVIII 500 (500 MHz) or AVIII 500 Ascend (500 MHz) spectrometer and are reported in ppm, relative to residual protonated solvent peak ($CHCl_3$, 7.26 ppm). Data are reported as follows: (bs= broad singlet, s = singlet, d = doublet, t = triplet, m = multiplet; coupling constant(s) in Hz; integration). Proton decoupled ^{13}C NMR spectra were recorded on a Bruker AVIII 500 (125 MHz) or AVIII 500 Ascend (125 MHz) spectrometer, relative to $CDCl_3$ (77.16 ppm). Gas chromatographic (GC) analyses were performed on a Hewlett-Packard 6890 Series Gas Chromatograph equipped with a capillary split-splitless inlet and flame ionization detector with electronic pneumatics control using a Supelco β-Dex 325 (30 m x 0.25 mm) capillary GLC column.

Cell culture and growth inhibition. DLD1 cells were obtained from ATCC (Manassas VA), and all other cell lines were obtained from the NCI anticancer drug screen. All cells were maintained in RPMI medium supplemented with 10% fetal bovine serum. Growth inhibition was determined by the sulforrhodamine B method, following exposure to serial dilutions of each compound for 4 days prior to fixation, staining and GI(50) determinations as described.[1] The results presented are mean values based on two or more determinations. The standard deviation (for three or more determinations) or half-range (for two values) were between 10% and 50% of the mean for all values.

Experimental Procedures



To a solution of (*S*,*S*)-allylsilane **7** (6.7g, 12 mmol, 1.1 equiv) and 6-chloro-1-hexene (3.2 mL, 24 mmol, 2.2 equiv) in $CHCl_3$ (60 mL, 0.2 M) was added 2nd generation Hoveyda-Grubbs catalyst (378 mg, 0.60 mmol, 5 mol%). The reaction mixture was heated to 70 °C. After 5h, the reaction mixture was cooled to 0 °C. Aldehyde **5** (1.4 g, 11 mmol, 1 equiv) was added, followed by scandium triflate (270 mg, 0.60 mmol, 5 mol%). After

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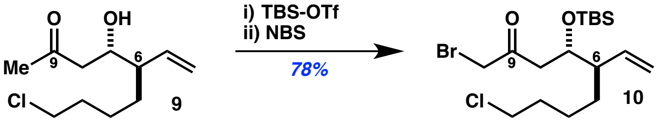
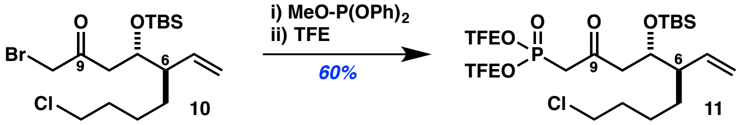
(1) Giannakakou, P., Sackett, D. L., Kang, Y. K., Zhan, Z., Buters, J. T., Fojo, T., Poruchynsky, M. S. Paclitaxel-resistant human ovarian cancer cells have mutant beta-tubulins that exhibit impaired paclitaxel-driven polymerization. *J. Biol. Chem.* **272**, 17118-17125 (1997).

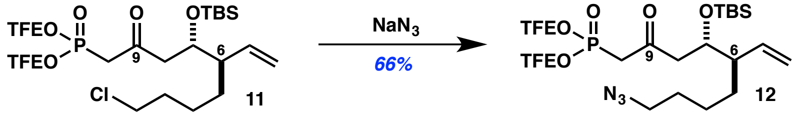
vigorously stirring for 2.5 h at 0 °C, the reaction mixture was concentrated, re-suspended in Et_2O (60 mL), and quenched at 0 °C with 1N HCl (60 mL). This acidic isolation serves both to hydrolyze the C9 ketal and protonate the diaminocyclohexane controller. After stirring overnight, the reaction mixture was filtered. The aqueous layer of the filtrate was separated and extracted with EtOAc (3x100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (10-40% EtOAc/Hex) affording methyl ketone **9** (1.4 g, 3:1 dr, 58% combined yield) as a dark red oil, presumably contaminated with ruthenium. A more complete purification was therefore performed after the following step. The enantiomeric excess of **9** was determined to be 90% ee by ^{1}H NMR and chiral GC analysis of the derived (*R*)-MTPA Mosher ester. **TLC** $R_f = 0.3$ (25% EtOAc/Hex); **IR** (thin film) 3446 (bs), 2935, 1707, 1359, 1000, 917, 733 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ (major diastereomer) 5.66 (dt, J = 17.3, 9.8 Hz, 1H, C_5H), 5.17 – 5.02 (m, 2H, C_4H_2), 4.03 (dt, J = 6.3, 3.4 Hz, 1H, C_7H), 3.51 (t, J = 6.7 Hz, 2H, α-Cl), 2.84 (d, J = 2.9 Hz, 1H, OH), 2.70 – 2.45 (m, 2H, C_8H_2), 2.16 (s, 3H, $C_{10}H_3$), 1.96 (app. tt, J = 8.9, 4.1 Hz, 1H, C_6H), 1.83 – 1.67 (m, 2H, β-Cl), 1.56 – 1.17 (m, 4H); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ (major diastereomer) 209.9, 138.0, 117.9, 69.7, 49.7, 48.0, 45.1, 32.7, 31.0, 30.1, 24.8; **HRMS:** Exact mass calcd for $C_{11}H_{19}ClNaO_2$ $[M+Na]^+$: 241.0971; found 241.0984 (TOF MS ES+).



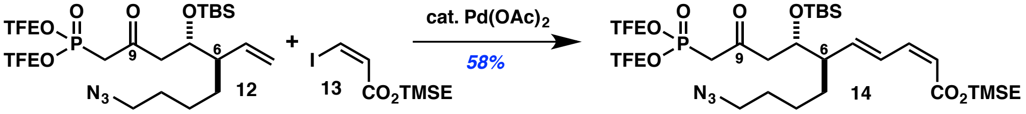
To a cooled (-78 °C) solution of ketone **9** (360 mg, 2.5:1 dr, 1.7 mmol, 1 equiv) in CH_2Cl_2 (17 mL, 0.1 M) was added 2,6-lutidine (778 µL, 6.9 mmol, 4.2 equiv) and freshly-distilled TBS-OTf (794 µL, 3.5 mmol, 2.1 equiv). The reaction mixture was allowed to warm to 0 °C as the dry ice bath expired. After 3h, the reaction mixture was re-cooled to -78 °C, and a solution of *N*-bromosuccinimide (352 mg, 2.0 mmol, 1.2 equiv) in THF (8.5 mL) was added over 30 min. After 3h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (1% EtOAc/Hex) affording bromoketone **10** as a mixture of C6 diastereomers (530 mg, 2.5:1 dr, 78% combined yield). This material was used without further purification, and the separation of diastereomers was performed at a later stage. **TLC** $R_f = 0.53$ (10% EtOAc/Hex, one spot); **IR** (thin film) 2930, 2857, 1717, 1462, 1253, 1074, 834, 776 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 5.62 (ddd, J = 17.3, 10.3, 9.1 Hz, 1H, C_5H major), 5.59 (ddd, J = 17.2, 10.3, 8.6 Hz, 1H, C_5H minor), 5.15 – 4.99 (m, 2H, C_4H_2), 4.19 (ddd, J = 6.8, 5.7, 3.0 Hz, 1H, C_7H major), 4.13 (ddd, J = 7.1, 5.5, 4.3 Hz, 1H, C_7H minor), 3.90 (s, 2H, $C_{10}H_2$ minor), 3.88 (s, 2H, $C_{10}H_2$ major), 3.51 (t, J = 6.7 Hz, 2H, α-Cl), 2.81 – 2.61 (m, 2H, C_8H_2), 2.16 – 2.10 (m, 1H, C_6H minor), 2.07 (app. tt, J = 9.3, 3.3 Hz, 1H, C_6H major), 1.83 – 1.67 (m, 2H), 1.58 – 1.43 (m, 2H), 1.37 – 1.19 (m, 2H), 0.87 (s, 9H, TBS), 0.08 (s, 3H, TBS), 0.01 (s, 3H, TBS); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ (major diastereomer) 200.7, 138.1, 117.8, 71.6, 50.0, 45.1, 44.7, 35.8, 32.8, 29.4, 26.0, 25.0, 18.2, -4.4, -4.5; **HRMS**: Exact mass calcd for $C_{17}H_{31}BrClO_2Si$ $[M–H]^-$: 409.0965; found 409.0971 (FAB+).



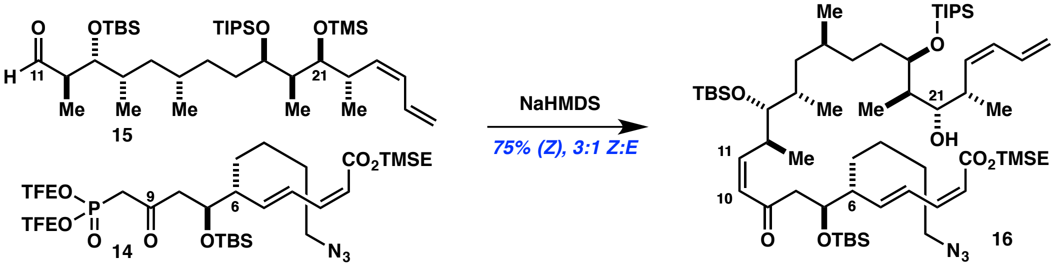
Bromoketone **10** (880 mg, 2.5:1 dr, 2.1 mmol, 1 equiv) and methyl-diphenylphosphite (686 µL, 3.2 mmol, 2 equiv) were combined together neat and heated to 140 °C. After 7h, aliquot ^{1}H-NMR indicated full conversion of bromoketone **10** (this reaction time may vary depending on the scale of the reaction). The reaction mixture was cooled to 0 °C. TFE (9.3 mL, 60 equiv), THF (4.7 mL), and DBU (479 µL, 3.2 mmol, 1.5 equiv) were added in that order. The reaction mixture was heated to 45 °C. After 1h, the reaction mixture was cooled to room temperature and filtered over a silica gel plug, eluting with 50% EtOAc/Hex (250 mL). The filtrate was concentrated and purified by silica gel flash column chromatography (2-20% EtOAc/Hex) affording TFE phosphonate **11** as a mixture of C6 diastereomers (732 mg, 2.5:1 dr, 60% combined yield). This material was used without further purification, and the separation of diastereomers was performed at a later stage. **TLC** R$_f$ = 0.4 (20% EtOAc/Hex); **IR** (thin film) 2932, 2859, 1718, 1294, 1259, 1169, 1069, 962, 836 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 5.65 – 5.51 (m, 1H, C_5H), 5.15 – 4.96 (m, 2H, C_4H_2), 4.48 – 4.37 (m, 4H, TFE), 4.16 (app. td, J = 6.1, 2.9 Hz, 1H, C_7H major), 4.09 (app. td, J = 6.3, 4.7 Hz, 1H, C_7H minor), 3.51 (t, J = 6.7 Hz, 2H, α-Cl), 3.34 – 3.17 (m, 2H, $C_{10}H_2$), 2.75 – 2.58 (m, 2H, C_8H_2), 2.14 – 2.01 (m, 1H, C_6H), 1.82 – 1.67 (m, 2H), 1.57 – 1.41 (m, 2H), 1.37 – 1.18 (m, 2H), 0.86 (s, 9H, TBS), 0.07 (s, 3H, TBS), 0.01 (s, 3H, TBS); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ (major diastereomer) 200.1 (d, $^2J_{C,P}$ = 7.0 Hz), 138.0, 122.6 (qd, J = 277.6, 8.6 Hz, 2C), 117.8, 70.9, 62.6 (qd, J = 38.1, 5.4 Hz), 62.5 (qd, J = 38.1, 5.3 Hz), 49.9, 49.1 (d, $^3J_{C,P}$ = 5.4 Hz), 45.0, 42.7 (d, $^1J_{C,P}$ = 138.8 Hz), 32.8, 29.3, 25.9, 25.0, 18.1, -4.5, -4.6; **HRMS**: Exact mass calcd for $C_{21}H_{35}ClF_6O_5PSi$ $[M–H]^-$: 575.1584; found 575.1602 (FAB+).



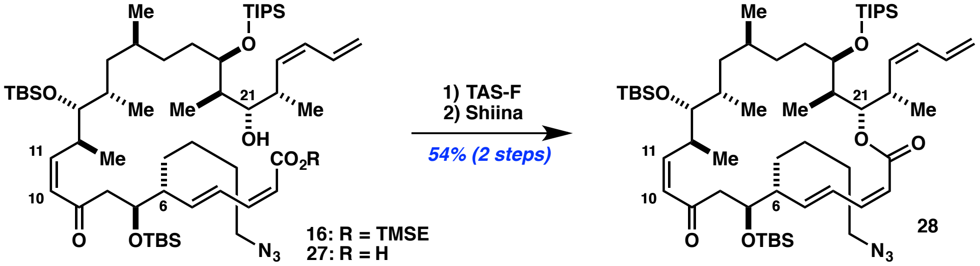
To a solution of chloride **11** (342 mg, 0.59 mmol, 1 equiv) in DMF (4 mL, 0.12 M) was added sodium azide (46 mg, 0.71 mmol, 1.2 equiv). The reaction mixture was heated to 70 °C. After 7h, aliquot ^{1}H-NMR indicated full conversion of starting material. The reaction mixture was allowed to cool to room temperature and directly purified by silica gel flash column chromatography (5-30% EtOAc/Hex) affording azide **12** as a mixture of C6 diastereomers (227 mg, 66% yield). This material was used without further purification, and the separation of diastereomers was performed at a later stage. **TLC** R$_f$ = 0.55 (30% EtOAc/Hex; product co-spots with starting material); **IR** (thin film) 2932, 2859, 2096, 1718, 1259, 1170, 1068, 836 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ (major diastereomer) 5.60 (ddd, J = 17.2, 10.3, 9.0 Hz, 1H, C_5H), 5.13 (dd, J = 10.3, 1.9 Hz, 1H, C_4H_a), 5.00 (dd, J = 17.2, 1.9 Hz, 1H, C_4H_b), 4.50 – 4.37 (m, 4H, TFE), 4.16 (app. td, J = 6.1, 2.9 Hz, 1H, C_7H), 3.29 – 3.21 (m, 4H, $C_{10}H_2$, α-N_3), 2.69 – 2.65 (m, 2H, C_8H_2), 2.06 (app. ddd, J = 12.8, 6.4, 3.4 Hz, 1H, C_6H), 1.66 – 1.48 (m, 3H), 1.45 – 1.20 (m, 3H), 0.87 (s, 9H, TBS), 0.08 (s, 3H, TBS), 0.02 (s, 3H, TBS); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ (major diastereomer) 200.1 (d, $^2J_{C,P}$ = 6.9 Hz), 138.0, 122.6 (qd, J = 277.5, 8.2 Hz, 2C), 117.9, 71.0, 62.6 (qd, J = 38.0, 5.4 Hz), 62.5 (qd, J = 37.9, 5.3 Hz), 51.5, 50.0, 49.2 (d, $^3J_{C,P}$ = 5.1 Hz), 42.8 (d, $^1J_{C,P}$ = 138.8 Hz), 30.0, 29.0, 25.9 (3C), 24.9, 18.2, -4.5, -4.5; **LRMS**: Exact mass calcd for $C_{21}H_{37}F_6N_3O_5PSi$ $[M+H]^+$: 584.2; found 584.2 (FAB+).



To a solution of phosphonate **12** (191 mg, 0.33 mmol, 1 equiv) and iodo-acrylate **13** (195 mg, 0.65 mmol, 2 equiv) in MeCN (3.3 mL, 0.1 M) was added AgOAc (109 mg, 0.65 mmol, 2 equiv) and $Pd(OAc)_2$ (2.2 mg, 0.0098 mmol, 3 mol%). The reaction mixture was heated to 45 °C. Additional $Pd(OAc)_2$ was added at t = 16h (2.2 mg, 3 mol%) and t = 24h (1.1 mg, 1.5 mol%; total of 7.5 mol%). After a total reaction time of 40h, the reaction mixture was cooled to room temperature and filtered over celite, eluting with 50% EtOAc/Hex (50 mL) The filtrate was washed with pH 7.0 buffer solution (20 mL). The aqueous layer was separated and extracted with 50% EtOAc/Hex (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (5-30% EtOAc/Hex) affording pure *cis*-dienoate **14** (74 mg, 30% yield) and a mixture of C6 epimers (68 mg, 28% yield; 58% combined yield). **TLC** R$_f$ = 0.50 (35% EtOAc/Hex); $[\alpha]^{22}_D$ -4.0 (c = 1.0, CH_2Cl_2); **IR** (thin film) 2953, 2858, 2096, 1713, 1254, 1172, 1069, 837 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.35 (dd, J = 15.5, 11.1 Hz, 1H, C_4H), 6.53 (t, J = 11.3 Hz, 1H, C_3H), 5.84 (dd, J = 15.5, 9.4 Hz, 1H, C_5H), 5.62 (d, J = 11.3 Hz, 1H, C_2H), 4.49 – 4.39 (m, 4H, TFE), 4.24 – 4.17 (m, 3H, TMSE, C_7H), 3.34 – 3.20 (m, 2H, $C_{10}H_2$), 3.25 (t, J = 6.9 Hz, 2H, α-N_3), 2.67 (app. d, J = 6.1 Hz, 2H, C_8H_2), 2.26 – 2.19 (m, 1H, C_6H), 1.64 – 1.52 (m, 3H), 1.44 – 1.32 (m, 2H), 1.32 – 1.24 (m, 1H), 1.04 – 0.99 (m, 2H, TMSE), 0.87 (s, 9H, TBS), 0.09 (s, 3H, TBS), 0.05 (s, 9H, TMSE), 0.02 (s, 3H, TBS); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 199.7 (d, $^2J_{C,P}$ = 6.9 Hz), 166.7, 144.3, 143.6, 129.6, 122.6 (qd, J = 277.5, 8.1 Hz, 2C), 117.3, 70.7, 62.5 (app. qt, J = 38.0, 5.9 Hz, 2C), 62.3, 51.4, 49.6 (d, $^3J_{C,P}$ = 4.9 Hz), 49.1, 42.7 (d, ${}^1J_{C,P}$ = 137.9 Hz), 30.3, 29.0, 26.0 (3C), 24.9, 18.2, 17.5, -1.4 (3C), -4.4, -4.6; **LRMS**: Exact mass calcd for $C_{29}H_{50}F_6N_3NaO_7PSi_2$ $[M+Na]^+$: 776.27; found 776.18 (FAB+).

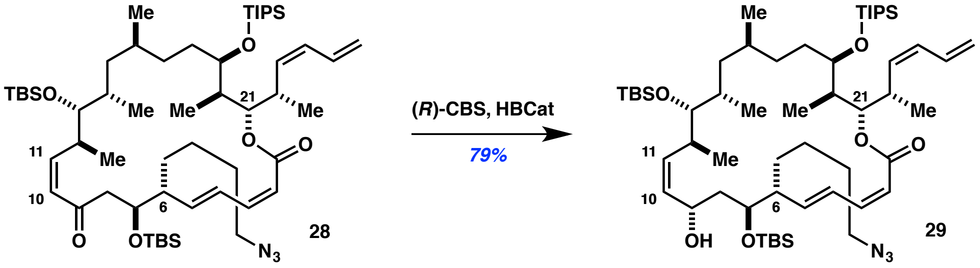


To a cooled (-78 °C) solution of phosphonate **14** (60 mg, 0.080 mmol, 1.5 equiv) in THF (1 mL, 0.05 M) was added NaHMDS (1M THF, 69 µL, 0.069 mmol, 1.3 equiv). After 20 min, aldehyde **15** (37 mg, 0.053 mmol, 1 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After 48h, the reaction mixture was quenched at 0 °C with a solution of PPTS (5 mg) in MeOH (2 mL). After 2h, the reaction mixture was diluted with pH 7.0 buffer solution (10 mL). The aqueous layer was separated and extracted with EtOAc (5x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (4% EtOAc/Hex) affording a 3:1 *Z*:*E* mixture of enone **16** (44 mg of *Z*-isomer, 75% yield of *Z*-isomer). **TLC** R_f = 0.50 (10% EtOAc/Hex); $[\alpha]^{22}_D$ -14.7 (*c* = 0.33, CH_2Cl_2); **IR** (thin film) 2930, 2862, 2095, 1713, 1637, 1604, 1461, 1251, 1172, 1059, 835, 774, 675 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 15.5, 11.3 Hz, 1H, C_4H), 6.66 (dt, *J* = 16.9, 10.6 Hz, 1H, $C_{25}H$), 6.57 (t, *J* = 11.3 Hz, 1H, C_3H), 6.32 (dd, *J* = 11.6, 9.7 Hz, 1H, $C_{11}H$), 6.09 (t, *J* = 11.0 Hz, 1H, $C_{24}H$), 6.03 (d, *J* = 11.7 Hz, 1H, $C_{10}H$), 5.94 (dd, *J* = 15.5, 9.4 Hz, 1H, C_5H), 5.61 (d, *J* = 11.3 Hz, 1H, C_2H), 5.49 (t, *J* = 10.3 Hz, 1H, $C_{23}H$), 5.21 (dd, *J* = 16.9, 2.0 Hz, 1H, $C_{26}H_a$), 5.12 (d, *J* = 10.3 Hz, 1H, $C_{26}H_b$), 4.31 (td, *J* = 6.0, 2.6 Hz, 1H, C_7H), 4.26 – 4.21 (m, 2H, TMSE), 4.01 – 3.93 (m, 1H, $C_{19}H$), 3.77 – 3.67 (m, 1H, $C_{12}H$), 3.60 – 3.56 (m, 1H, $C_{21}H$), 3.50 (app. t, *J* = 3.4 Hz, 1H, $C_{13}H$), 3.26 (t, *J* = 7.0 Hz, 2H, α-N_3), 2.88 – 2.80 (m, 1H, $C_{22}H$), 2.78 (d, *J* = 1.7 Hz, 1H, OH), 2.61 – 2.50 (m, 2H, C_8H_2), 2.27 – 2.19 (m, 1H, C_6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.3, 166.7, 152.5, 144.8, 144.6, 135.9, 132.6, 129.6, 129.3, 125.4, 117.6, 116.7, 79.9, 79.3, 78.5, 71.0, 62.2, 51.5, 50.1, 49.5, 41.2, 37.4, 36.5, 36.2, 36.1, 32.7, 31.9, 30.9, 30.9, 29.1, 26.3, 26.1, 25.0, 20.7, 19.3, 18.6, 18.5, 18.4, 18.2, 18.0, 17.6, 15.9, 13.6, 5.9, -1.3, -3.5, -3.8, -4.1, -4.6. **HRMS:** Exact mass calcd for $C_{61}H_{118}N_3O_7Si_4$ $[M+H]^+$: 1116.8047; found 1116.7997 (TOF MS ASAP+).

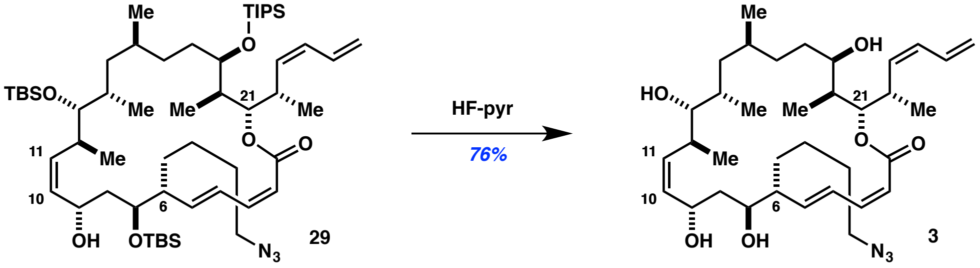


C1 Deprotection: To a cooled (0 °C) solution of TMSE ester **16** (44 mg, 0.039 mmol, 1 equiv) in DMF (3.9 mL, 0.01M) was added a solution of TAS-F (11 mg, 0.041, 1.05 equiv) in DMF (0.5 mL) dropwise. The reaction mixture was allowed to warm to room temperature. After 20h, the reaction mixture was diluted with Et_2O (10 mL) and quenched at 0 °C with 1M $NaHSO_4$ (5 mL). The reaction mixture was further diluted with saturated aqueous NaCl (5 mL) and extracted with Et_2O (5x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford acid **27**, which was used immediately without purification.

*Macrolactonization***:** To a solution of crude acid **27** in Toluene (39 mL, 0.001M) was added 2-methyl-6-nitrobenzoic anhydride (41 mg, 0.12 mmol, 3 equiv), DMAP (5 mg, 0.039 mmol, 1 equiv), and NEt_3 (55 µL, 0.39 mmol, 10 equiv). After 24h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) The aqueous layer was separated and extracted with EtOAc (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (1-5% EtOAc/Hex) affording macrocycle **28** (21 mg, 54% yield over 2 steps). **TLC** R_f = 0.52 (10% EtOAc/Hex); **[α]**$^{19}_{\mathbf{D}}$ -9.7 (*c* = 1.0, CH_2Cl_2); **IR** (thin film) 2931, 2864, 2096, 1707, 1462, 1380, 1255, 1051, 836, 775 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 15.6, 11.1 Hz, 1H, C_4H), 6.62 – 6.52 (m, 2H, $C_{25}H$, C_3H), 6.38 (dd, *J* = 11.7, 10.2 Hz, 1H, $C_{11}H$), 6.09 (d, *J* = 11.7 Hz, 1H, $C_{10}H$), 6.04 (t, *J* = 11.2 Hz, 1H, $C_{24}H$), 5.91 (dd, *J* = 15.5, 9.0 Hz, 1H, C_5H), 5.61 (d, *J* = 11.6 Hz, 1H, C_2H), 5.47 (t, *J* = 10.8 Hz, 1H, $C_{23}H$), 5.36 (dd, *J* = 9.1, 2.9 Hz, 1H, $C_{21}H$), 5.21 (d, *J* = 16.8 Hz, 1H, $C_{26}H_a$), 5.13 (d, *J* = 10.6 Hz, 1H, $C_{26}H_b$), 4.17 – 4.11 (m, 1H, C_7H), 3.89 – 3.80 (m, 1H, $C_{19}H$), 3.80 – 3.69 (m, 1H, $C_{12}H$), 3.32 (dd, *J* = 5.7, 2.0 Hz, 1H, $C_{13}H$), 3.26 (t, *J* = 7.0 Hz, 2H, α-N_3), 3.19 – 3.11 (m, 1H, $C_{22}H$), 2.61 (dd, *J* = 13.8, 6.8 Hz, 1H, C_8H_a), 2.45 (dd, *J* = 13.8, 4.9 Hz, 1H, C_8H_b), 2.13 (m, 1H, C_6H); **^{13}C NMR** not included due to rotamers causing significant line broadening; **LRMS**: Exact mass calcd for $C_{53}H_{103}N_3NaO_6Si_3$ $[M+Na]^+$: 1020.7; found 1020.8 (FAB+).

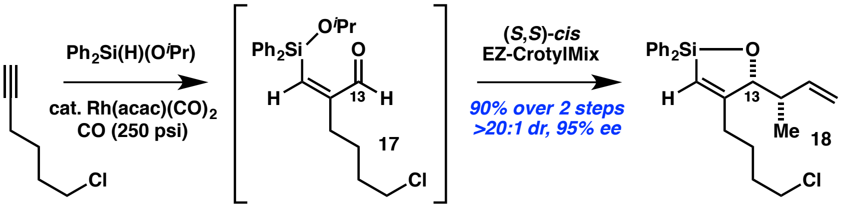


To a cooled (-78 °C) solution of enone **28** (18 mg, 18 μmol, 1 equiv) in Toluene (360 μL, 0.05M) was added (*R*)-2-Methyl-CBS oxazaborolidine (1M Tol, 90 μL, 90 μmol, 5 equiv) and catecholborane (50% w/w Toluene, 50 μL, 0.18 mmol, 10 equiv). After 24h at -78 °C, the reaction mixture was quenched with MeOH (2 mL), followed by saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was separated and extracted with Et_2O (5x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (5-10% EtOAc/Hex) affording allylic alcohol **29** (14 mg, 79% yield). **TLC** R_f = 0.32 (10% EtOAc/Hex); **[α]**$^{22}_{\mathbf{D}}$ -114 (*c* = 0.1, CH_2Cl_2); **IR** (thin film) 3492, 2930, 2863, 2096, 1711, 1462, 1254, 1052, 836, 775, 678 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 15.4, 11.4 Hz, 1H, C_4H), 6.57 (dt, *J* = 16.9, 10.5 Hz, 1H, $C_{25}H$), 6.52 (t, *J* = 11.4 Hz, 1H, C_3H), 6.06 (t, *J* = 11.1 Hz, 1H, $C_{24}H$), 5.98 (dd, *J* = 15.7, 7.6 Hz, 1H, C_5H), 5.69 (t, *J* = 9.9 Hz, 1H, $C_{11}H$), 5.60 (d, *J* = 11.4 Hz, 1H, C_2H), 5.43 – 5.35 (m, 2H, $C_{23}H$, $C_{10}H$), 5.28 – 5.17 (m, 2H, $C_{21}H$, $C_{26}H_a$), 5.09 (d, *J* = 9.6 Hz, 1H, $C_{26}H_b$), 4.55 (t, *J* = 9.5 Hz, 1H, C_9H), 4.05 (dt, *J* = 9.9, 2.9 Hz, 1H, C_7H), 3.77 (bs, 1H, $C_{19}H$), 3.23 (m, 3H, $C_{13}H$, α-N_3), 3.08 (bs, 1H, $C_{22}H$), 2.73 – 2.64 (m, 1H, $C_{12}H$), 2.31 (bs, 1H, C_6H), 1.86 (bs, 1H, $C_{20}H$); **^{13}C NMR** not included due to rotamers causing substantial line broadening; **HRMS:** Exact mass calcd for $C_{56}H_{104}N_3O_5Si_3$ $[M+H-H_2O]^+$: 982.7284; found 982.7284 (TOF MS ASAP+).



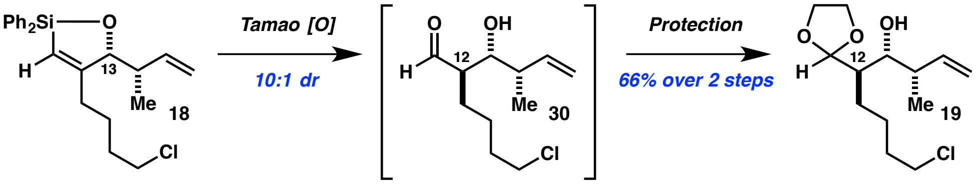
To a cooled (0 °C) solution of **29** (14 mg) in THF (2 mL) in a Nalgene tube was added HF-pyridine (100 μL). The reaction mixture was allowed to warm to room temperature. At t = 24h, 48h, and 60h, additional HF-pyridine (100 μL; total of 400 μL) was added. After a total reaction time of 90h, the reaction mixture was slowly quenched at 0 °C with saturated aqueous $NaHCO_3$ (10 mL) and then diluted with CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (5x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (50-100% EtOAc/Hex) affording **3** (6.5 mg, 76% yield). **TLC** R_f = 0.48 (80% EtOAc/Hex); **[α]**$^{18}_{\mathbf{D}}$ 48.5 (*c* = 0.1,

CH_2Cl_2); **IR** (thin film) 3403, 2925, 2096, 1694, 1456, 1277, 1042, 961 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (dd, J = 15.8, 11.3 Hz, 1H, C_4H), 6.64 – 6.55 (m, 1H, $C_{25}H$), 6.49 (t, J = 11.3 Hz, 1H, C_3H), 6.02 (dd, J = 15.9, 7.4 Hz, 1H, C_5H), 5.99 (t, J = 11.0 Hz, 1H, $C_{24}H$), 5.57 (t, J = 10.2 Hz, 1H, $C_{10}H$), 5.49 (d, J = 11.3 Hz, 1H, C_2H), 5.34 (t, J = 10.5 Hz, 1H, $C_{11}H$), 5.26 (t, J = 10.5 Hz, 1H, $C_{23}H$), 5.18 (dd, J = 16.9, 1.9 Hz, 1H, $C_{26}H_a$), 5.10 (d, J = 10.1 Hz, 1H, $C_{26}H_b$), 4.94 (dd, J = 8.2, 2.6 Hz, 1H, $C_{21}H$), 4.81 (dt, J = 10.4, 5.7 Hz, 1H, C_9H), 4.01 – 3.96 (m, 1H, C_7H), 3.51 – 3.46 (m, 1H, $C_{19}H$), 3.30 – 3.24 (m, 3H, $C_{13}H$, α-N_3), 3.04 – 2.94 (m, 1H, $C_{22}H$), 2.81 – 2.70 (m, 1H, $C_{12}H$), 2.27 – 2.20 (m, 1H, C_6H), 1.91 – 1.83 (m, 1H, $C_{20}H$), 1.06 (d, J = 6.8 Hz, 3H, $C_{20}CH_3$), 1.00 (d, J = 6.7 Hz, 3H, $C_{22}CH_3$), 0.94 (app. t, J = 6.5 Hz, 6H, $C_{12}CH_3$, $C_{14}CH_3$), 0.90 (d, J = 6.4 Hz, 3H, $C_{16}CH_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.7, 145.7, 145.2, 134.9, 134.0, 133.0, 132.2, 130.3, 128.5, 118.1, 116.3, 76.3, 76.2, 73.3, 70.1, 66.5, 51.5, 47.5, 42.4, 40.0, 38.9, 35.3, 35.3, 32.1, 31.6, 31.4, 29.9, 29.5, 29.3, 24.5, 21.3, 17.8, 17.6, 14.2, 10.4; **HRMS:** Exact mass calcd for $C_{35}H_{55}N_3NaO_5$ $[M+Na-H_2O]^+$: 620.4039; found 620.4043 (TOF MS ES+).

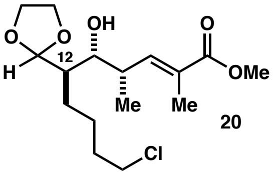


Silylformylation: To the glass liner of a Parr bomb was added 6-chloro-1-hexyne (5.0 g, 43 mmol, 1 equiv), diphenyl-isopropoxy-silane (10 g, 4.3 mmol, 1 equiv), and benzene (43 mL, 1M). The glass liner was cooled to -78 °C, and $Rh(acac)(CO)_2$ (111 mg, 0.043 mmol, 1 mol%) was added on top of the frozen benzene solution. While frozen, the glass liner was quickly placed into the Parr bomb, which was then charged to 250 psi with CO (vented and re-charged 3X). After 6h, aliquot ^{1}H-NMR indicated full conversion of 6-chloro-1-hexyne to aldehyde **17**. The reaction mixture was concentrated and aldehyde **17** was used immediately without purification.

Crotylation: To a solution of crude aldehyde **17** in CH_2Cl_2 (214 mL, 0.2 M) was added (*S*,*S*)-*cis*-crotylsilane (27 g, 47 mmol, 1.1 equiv), followed by $Sc(OTf)_3$ (633 mg, 1.3 mmol, 3 mol%). After vigorously stirring for 3h, the reaction mixture was quenched at 0 °C with TBAF (47 mL, 1M THF) and allowed to warm to room temperature. After 1h, the reaction mixture was concentrated and filtered over a plug of silica gel, eluting with 50% EtOAc/Hex (2L). The filtrate was then concentrated and purified by silica gel flash column chromatography (1-5% EtOAc/Hex) affording vinylsilane **18** (15 g, 90% yield over 2 steps). The enantiomeric excess of **18** was determined to be 95% ee by ^{1}H NMR of the derived (*R*)-MTPA Mosher ester of acetal **19**. Aldehyde **17**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.02 (s, 1H, CHO), 7.65 – 7.60 (m, 4H), 7.49 – 7.36 (m, 6H), 7.08 (t, J = 1.3 Hz, 1H, $C_{11}H$), 4.13 (hept, J = 6.1 Hz, 1H, -O*i*Pr), 3.55 (t, J = 6.6 Hz, 2H, α-Cl), 2.41 (td, J = 7.7, 1.3 Hz, 2H), 1.86 – 1.77 (m, 2H), 1.71 – 1.60 (m, 2H), 1.16 (d, J = 6.1 Hz, 6H). Vinylsilane **18**: **TLC** R_f = 0.6 (10% EtOAc/Hex); **$[\alpha]^{19}_D$** -20.7 (c = 2.0, CH_2Cl_2); **IR** (thin film) 3068, 2934, 1580, 1428, 1113, 996, 822, 739, 699 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 – 7.63 (m, 2H), 7.53 – 7.50 (m, 2H), 7.47 – 7.32 (m, 6H), 6.09 (ddd, J = 16.5, 9.8, 6.7 Hz, 1H, $C_{15}H$), 6.05 (d, J = 1.7 Hz, 1H, $C_{11}H$), 5.14 – 5.05 (m, 2H, $C_{16}H_2$), 4.87 (t, J = 2.1 Hz, 1H, $C_{13}H$), 3.59 (t, J = 6.4 Hz, 2H, α-Cl), 2.59 – 2.52 (m, 1H, $C_{14}H$), 2.31 – 2.16 (m, 2H), 1.91 – 1.84 (m, 2H), 1.84 – 1.76 (m, 2H), 0.76 (d, J = 6.9 Hz, 3H, $C_{14}CH_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.0, 142.6, 135.8, 135.1, 135.0, 134.7, 130.2, 127.9, 127.9, 119.2, 114.0, 88.3, 45.0, 40.9, 32.4, 31.5, 25.0, 12.3; **HRMS**: Exact mass calcd for $C_{23}H_{26}OClSi$ $[M–H]^-$: 381.1441; found 381.1448 (FAB+).

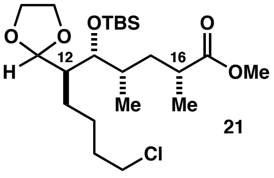


Tamao oxidation: To a cooled (0 °C) solution of vinylsilane **18** (2.5 g, 6.5 mmol, 1 equiv) in 1:1 THF / ^{i}PrOH (65 mL, 0.1 M) was added $KHCO_3$ (686 mg, 6.9 mmol, 1.05 equiv), followed by H_2O_2 (8.5 mL, 85 mmol, 13 equiv, 30% wt in H_2O). After 3h at 0 °C, the reaction mixture was quenched with H_2O (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford aldehyde **30**, which was used immediately without purification.
Protection: To a solution of crude aldehyde **30** in Toluene (65 mL, 0.1M) was added ethylene glycol (3.7 mL, 65 mmol, 10 equiv) and PPTS (1.6 g, 6.5 mmol, 1 equiv). The reaction mixture was heated to 100 °C. After 1h, the reaction mixture was cooled to room temperature and concentrated to *ca.* 10 mL. Purification was accomplished by silica gel flash column chromatography affording acetal **19** as a mixture of C12 diastereomers (1.14 g, 10:1 dr, 66% combined yield). This material was used without further purification, and the separation of diastereomers was performed at a later stage. Aldehyde **30:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (d, J = 2.5 Hz, 1H, CHO), 5.78 – 5.66 (m, 1H, $C_{15}H$), 5.13 – 5.06 (m, 2H, $C_{16}H_2$), 3.64 (t, J = 5.9 Hz, 1H, $C_{13}H$), 3.53 (t, J = 6.5 Hz, 2H, α-Cl), 2.60 – 2.53 (m, 1H, $C_{12}H$), 2.47 – 2.40 (m, 1H, $C_{14}H$), 1.84 – 1.72 (m, 2H), 1.65 – 1.44 (m, 4H), 1.09 (d, J = 6.8 Hz, 3H, $C_{14}CH_3$). Acetal **19: TLC** R_f = 0.38 (25% EtOAc/Hex); **IR** (thin film) 3523 (bs), 2877, 1639, 1458, 1406, 1100, 999, 915 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.74 (ddd, J = 17.3, 10.4, 8.1 Hz, 1H, $C_{15}H$), 5.12 – 4.93 (m, 3H, $C_{16}H_2$, $C_{11}H$), 4.06 – 3.94 (m, 2H), 3.93 – 3.80 (m, 2H), 3.54 (td, J = 6.7, 1.5 Hz, 2H, α-Cl), 3.49 (dd, J = 7.5, 4.8 Hz, 1H, $C_{13}H$), 2.82 (bs, 1H, OH), 2.40 (app. hept, J = 7.0 Hz, 1H, $C_{14}H$), 2.00 – 1.94 (m, 1H, $C_{12}H$), 1.83 – 1.72 (m, 2H), 1.64 – 1.40 (m, 4H), 1.10 (d, J = 6.7, 3H, $C_{14}CH_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.7, 114.9, 104.9, 75.0, 65.2, 64.8, 45.1, 42.5, 42.2, 33.1, 24.9, 24.8, 16.2; **HRMS**: Exact mass calcd for $C_{13}H_{22}O_3Cl$ [M–H]$^-$: 261.1257; found 261.1269 (FAB+).



20

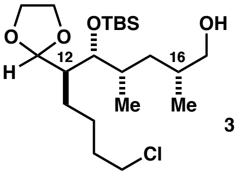
To a cooled (-78 °C) solution of **19** (1.0 g, 10:1 dr, 3.8 mmol, 1 equiv) in CH_2Cl_2 (38 mL, 0.1 M) was bubbled in ozone. Immediately after the solution began turning blue, the reaction mixture was purged with oxygen until colorless. PPh_3 (1.1 g, 4.2 mmol, 1.1 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After 12h, the reaction mixture was diluted with Toluene (38 mL). Freshly prepared phosphonium **A** (1.6 g, 4.6 mmol, 1.2 equiv) was added, and the reaction mixture was heated to 45 °C. After 5h, additional phosphonium **A** (1.6 g, 1.2 equiv) was added. After a total reaction time of 24h, the reaction mixture was cooled to room temperature and concentrated to *ca.* 10 mL. Purification was accomplished by silica gel flash column chromatography (10-40% EtOAc/Hex) affording methyl ester **20** (1.05 g, 10:1 dr, 83% combined yield). This material was used without further purification, and the separation of diastereomers was performed at a later stage. **TLC** R_f = 0.37 (30% EtOAc/Hex); **IR** (thin film) 3515 (bs), 2951, 2873, 1710, 1436, 1273, 1225, 1123, 1101, 988, 752 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.59 (dd, J = 10.2, 1.5 Hz, 1H, $C_{15}H$), 4.89 (d, J = 3.3 Hz, 1H, $C_{11}H$, 4.04 – 3.92 (m, 2H), 3.92 – 3.80 (m, 2H), 3.72 (s, 3H, CO_2Me), 3.58 – 3.48 (m, 3H, $C_{13}H$, α-Cl), 2.93 (d, J = 7.4 Hz, 1H, OH), 2.80 – 2.66 (m, 1H, $C_{14}H$), 1.85 (d, J = 1.5 Hz, 3H, $C_{16}CH_3$), 1.83 – 1.68 (m, 3H, $C_{12}H$), 1.59 – 1.42 (m, 4H), 1.09 (d, J = 6.6 Hz, 3H, $C_{12}CH_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.6, 144.3, 127.0, 104.9, 75.0, 65.1, 64.7, 51.8, 44.9, 43.3, 37.9, 32.9, 25.3, 24.6, 16.1, 12.7; **HRMS**: Exact mass calcd for $C_{16}H_{26}ClO_5$ [M–H]$^-$: 333.1469; found 333.1481 (FAB+).



21

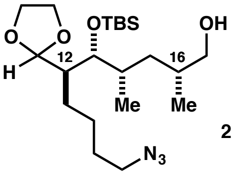
To the glass liner of a Parr bomb was added methyl ester **20** (1.1 g, 3.3 mmol, 1 equiv) and CH_2Cl_2 (8.2 mL, 0.4M). The Parr bomb was charged with H_2 (300 psi) and stirred overnight in order to saturate the solution.

Then, Crabtree's catalyst (53 mg, 0.066 mmol, 2 mol%) was added, and the bomb was charged to 300 psi with H_2. After 20h, additional Crabtree's catalyst (12 mg) was added. After a total reaction time of 36h, aliquot ^{1}H-NMR indicated full conversion of the major C12 diastereomer; the minor C12 diastereomer was not appreciably reduced. The glass liner was removed from the bomb and cooled to -78 °C. 2,6-lutidine (1.5 mL, 13 mmol, 4 equiv) and TBS-OTf (1.5 mL, 6.6 mmol, 2 equiv) were added, and the reaction mixture was allowed to warm to 0 °C as the dry ice bath expired. After 4h, the reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (2-5% EtOAc/Hex) affording a mixture of product **21** and the minor C12 diastereomer starting material (1.25 g, 84% combined yield). This material was used without further purification, and the separation was performed at a later stage. **TLC** R_f = 0.33 (10% EtOAc/Hex); **IR** (thin film) 2953, 2931, 1736, 1461, 1253, 1059, 835, 773 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 4.84 (d, *J* = 4.0 Hz, 1H, $C_{11}H$), 3.98 – 3.89 (m, 2H), 3.84 – 3.76 (m, 2H), 3.69 (dd, *J* = 5.9, 2.4 Hz, 1H, $C_{13}H$), 3.65 (s, 3H), 3.52 (t, *J* = 6.7 Hz, 2H, α-Cl), 2.60 – 2.45 (m, 1H, $C_{16}H$), 1.85 – 1.78 (m, 1H, $C_{12}H$), 1.78 – 1.64 (m, 4H), 1.61 – 1.39 (m, 5H, $C_{15}H_a$), 1.24 (m, 1H, $C_{15}H_b$), 1.15 (d, *J* = 6.9 Hz, 3H, $C_{16}CH_3$), 0.89 (s, 9H, TBS), 0.88 (d, *J* = 6.9 Hz, 3H, $C_{14}CH_3$), 0.06 (s, 3H, TBS), 0.05 (s, 3H, TBS); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 177.4, 105.2, 75.7, 64.9, 64.5, 51.6, 46.9, 45.1, 40.3, 37.5, 34.0, 33.4, 26.6, 26.3, 25.1, 18.6, 18.1, 14.5, -4.0, -4.0; **HRMS**: Exact mass calcd for $C_{22}H_{42}ClO_5Si$ [M–H]$^-$: 449.2490; found 449.2479 (FAB+).



31

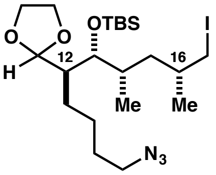
To a cooled (-78 °C) solution of ester **21** (1.25 g, 2.8 mmol, 1 equiv) in Toluene (28 mL, 0.1M) was added DIBAL (1M Hex, 7.6 mL, 7.6 mmol, 2.7 equiv) dropwise. After 4h, the reaction mixture was quenched with MeOH (10 mL), followed by a saturated aqueous solution of Rochelle's salt (50 mL). After vigorously stirring for 1h, the aqueous layer was separated and extracted with 50% EtOAc/Hex (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (10-20% EtOAc/Hex) affording pure alcohol **31** (1.04 g, 89% yield). **TLC** R_f = 0.47 (39% EtOAc/Hex); $[\alpha]^{21}_D$ -10.2 (*c* = 0.8, CH_2Cl_2); **IR** (thin film) 3393 (bs), 2928, 2857, 1462, 1251, 1059, 834, 772 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 4.85 (d, *J* = 4.4 Hz, 1H, $C_{11}H$), 3.97 – 3.90 (m, 2H), 3.84 – 3.77 (m, 2H), 3.65 (dd, *J* = 5.0, 3.4 Hz, 1H, $C_{13}H$), 3.53 (t, *J* = 6.7 Hz, 2H, α-Cl), 3.50 (dd, *J* = 10.8, 4.4 Hz, 1H, $C_{17}H_a$), 3.45 (dd, *J* = 10.8, 6.0 Hz, 1H, $C_{17}H_b$), 1.89 – 1.66 (m, 5H, $C_{12}H$, $C_{14}H$, β-Cl, $C_{16}H$), 1.57 – 1.37 (m, 5H, $C_{15}H_a$), 0.98 – 0.93 (m, 1H, $C_{15}H_b$), 0.94 (d, *J* = 6.7 Hz, 2H, $C_{16}CH_3$), 0.90 (s, 9H, TBS), 0.89 (d, *J* = 6.8 Hz, 3H, $C_{14}CH_3$), 0.06 (s, 3H, TBS), 0.05 (s, 3H, TBS); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 105.3, 75.8, 67.6, 64.8, 64.5, 46.8, 45.1, 39.0, 33.3, 33.3, 33.1, 26.6, 26.3, 25.5, 18.6, 18.0, 15.8, -3.8, -3.9; **HRMS**: Exact mass calcd for $C_{21}H_{43}ClNaO_4Si$ [M+Na]$^+$: 445.2517; found 445.2517 (FAB+).



22

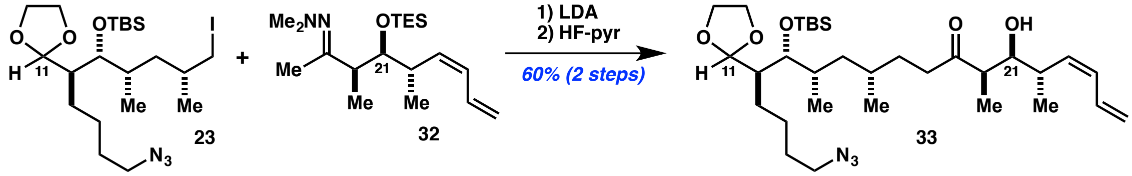
To a solution of chloride **31** (120 mg, 0.28 mmol, 1 equiv) in DMF (1.9 mL, 0.15 M) was added NaN_3 (20 mg, 0.31 mmol, 1.1 equiv). The reaction mixture was heated to 70 °C. After 6h, aliquot ^{1}H NMR indicated full conversion of starting material. The reaction mixture was allowed to cool to room temperature and directly purified by silica gel flash column chromatography (5-20% EtOAc/Hex) affording azide **22** (120 mg, 98% yield). **TLC** R_f = 0.47 (39% EtOAc/Hex; product co-spots with starting material); $[\alpha]^{18}_D$ -5.9 (*c* = 2.0, CH_2Cl_2); **IR** (thin film) 3359 (bs), 2929, 2858, 2094, 1462, 1252, 1063, 835, 773 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ

4.85 (d, *J* = 4.4 Hz, 1H, $C_{11}H$), 3.98 – 3.89 (m, 2H), 3.84 – 3.77 (m, 2H), 3.66 (dd, *J* = 5.1, 3.3 Hz, 1H, $C_{13}H$), 3.50 (dd, *J* = 10.8, 4.5 Hz, 1H, $C_{17}H_a$), 3.46 (dd, *J* = 10.8, 6.0 Hz, 1H, $C_{17}H_b$), 3.26 (t, *J* = 6.9 Hz, 2H, α-N_3), 1.88 – 1.77 (m, 2H, $C_{12}H$, $C_{14}H$), 1.74 – 1.66 (m, 1H, $C_{16}H$), 1.63 – 1.57 (m, 2H, β-N_3), 1.53 – 1.38 (m, 5H, $C_{15}H_a$), 0.98 – 0.93 (m, 1H, $C_{15}H_b$), 0.94 (d, *J* = 6.7 Hz, 3H, $C_{16}CH_3$), 0.90 (s, 9H, TBS), 0.89 (d, *J* = 6.9 Hz, 3H, $C_{14}CH_3$), 0.06 (s, 3H, TBS), 0.05 (s, 3H, TBS); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 105.3, 75.8, 67.6, 64.8, 64.5, 51.5, 46.9, 39.0, 33.3, 33.1, 29.5, 26.5, 26.3, 25.8, 18.6, 18.0, 15.9, -3.8, -3.9; **HRMS**: Exact mass calcd for $C_{21}H_{44}N_3O_4Si$ $[M+H]^+$: 430.3101; found 430.3109 (FAB+).



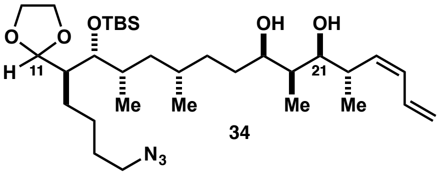
23

To a cooled (0 °C) solution of PPh_3 (714 mg, 2.7 mmol, 1.8 equiv) and imidazole (515 mg, 7.6 mmol, 5 equiv) in CH_2Cl_2 (5.6 mL) was added iodine (729 mg, 2.9 mmol, 1.9 equiv). After 10 min, a solution of alcohol **22** (640 mg, 1.5 mmol, 1 equiv) in CH_2Cl_2 (2 mL; final volume 7.6 mL, 0.2 M) was added, and the reaction mixture was allowed to warm to room temperature. After 12h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and quenched with saturated aqueous sodium thiosulfate (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (1-5% EtOAc/Hex) affording iodide **23** (740 mg, 92% yield). **TLC** R_f = 0.56 (10% EtOAc/Hex); **$[\alpha]^{17}_D$** -14.8 (*c* = 2.0, CH_2Cl_2); **IR** (thin film) 2928, 2861, 2093, 1461, 1251, 1067, 1032, 835, 773 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.85 (d, *J* = 4.2 Hz, 1H, $C_{11}H$), 3.99 – 3.90 (m, 2H), 3.84 – 3.78 (m, 2H), 3.68 (dd, *J* = 5.8, 2.6 Hz, 1H, $C_{13}H$), 3.29 – 3.23 (m, 3H, $C_{17}H_a$, α-N_3, 3.15 (dd, *J* = 9.7, 5.9 Hz, 1H, $C_{17}H_b$), 1.85 – 1.80 (m, 1H, $C_{12}H$), 1.79 – 1.70 (m, 1H, $C_{14}H$), 1.63 – 1.56 (m, 2H, β-N_3), 1.53 – 1.37 (m, 5H, $C_{16}H$), 1.31 (ddd, *J* = 13.3, 7.8, 5.3 Hz, 1H, $C_{15}H_a$), 1.11 (ddd, *J* = 13.5, 8.8, 6.0 Hz, 1H, $C_{15}H_b$), 0.97 (d, *J* = 6.5 Hz, 3H, $C_{16}CH_3$), 0.90 (s, 9H, TBS), 0.87 (d, *J* = 6.7 Hz, 3H, $C_{14}CH_3$), 0.07 (s, 3H, TBS), 0.06 (s, 3H, TBS); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 105.1, 75.6, 64.8, 64.4, 51.3, 46.9, 42.4, 33.0, 31.5, 29.4, 26.4, 26.1, 25.4, 21.6, 18.4, 18.1, 14.5, -4.1 (2C); **HRMS**: Exact mass calcd for $C_{21}H_{41}IN_3O_3Si$ $[M–H]^-$: 538.1962; found 538.1923 (FAB+).



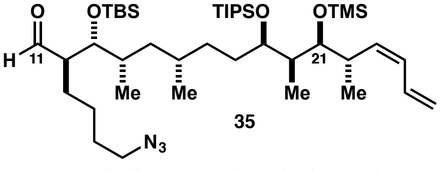
Hydrazone Alkylation: To a cooled (-10 °C) solution of *i*Pr_2NH (61 μL, 0.43 mmol, 1.8 equiv) in THF (600 μL, 0.4 M) was added MeLi (1.3 M Et_2O, 600 μL, 0.39 mmol, 1.6 equiv) under Argon. After 10 min, hydrazone **32** (122 mg, 0.36 mmol, 1.5 equiv) was added. After an additional 30 min, the reaction was cooled to -78 °C and DMPU (120 μL) was added, followed by iodide **23** (130 mg, 0.24 mmol, 1 equiv). The resulting solution was allowed to warm to -20 °C. After 15h at -20 °C, the reaction mixture was quenched with pH 7.0 buffer solution (4 mL). The aqueous layer was separated and extracted with EtOAc (5x20 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (4-10% EtOAc/Hex) affording the coupled adduct, which was contaminated with a small amount of unreacted iodide **23**. This mixture was used without further purification.

Deprotection: To a cooled (0 °C) solution of the coupled adduct in 9:1 THF/H_2O (2.5 mL) in a Nalgene tube was added 1 mL of a freshly prepared HF-pyr solution buffered with excess pyridine (stock solution prepared from 500 μL HF-pyr, 1 mL pyridine, and 4 mL THF). The reaction was allowed to warm to room temperature. After 8h, additional HF-pyr (50 μL) was added. After a total reaction time of 20h, the reaction mixture was quenched at 0 °C with pH 7.0 buffer solution (10 mL). The aqueous layer was separated and extracted with EtOAc (5x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (4-10% EtOAc/Hex to elute unreacted iodide **23**, then 10-20% EtOAc/Hex) affording keto-alcohol **33** (86 mg, 60% yield over 2 steps). **TLC** R_f = 0.39 (20% EtOAc/Hex); $[\alpha]^{23}_D$ 3.9 (*c* = 1.3, CH_2Cl_2); **IR** (thin film) 3498 (bs), 2955, 2928, 2095, 1707, 1461, 1377, 1252, 1062, 836, 773 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.56 (dt, *J* = 16.9, 10.6 Hz, 1H, $C_{25}H$), 6.11 (t, *J* = 10.9 Hz, 1H, $C_{24}H$), 5.39 (t, *J* = 10.5 Hz, 1H, $C_{23}H$), 5.23 (d, *J* = 16.7 Hz, 1H, $C_{26}H_a$), 5.13 (d, *J* = 10.2 Hz, 1H, $C_{26}H_b$), 4.83 (d, *J* = 4.1 Hz, 1H, $C_{11}H$), 3.98 – 3.88 (m, 2H), 3.83 – 3.76 (m, 2H), 3.75 – 3.71 (m, 1H, $C_{21}H$), 3.67 (dd, *J* = 5.2, 1.8 Hz, 1H, $C_{13}H$), 3.25 (t, *J* = 6.9 Hz, 2H, α-N_3), 2.80 – 2.71 (m, 1H, $C_{22}H$), 2.70 – 2.64 (m, 1H, $C_{20}H$), 2.47 (t, *J* = 7.7 Hz, 2H, $C_{18}H_2$), 2.39 – 2.27 (bs, 1H, OH), 1.84 – 1.73 (m, 2H, $C_{12}H$, $C_{14}H$), 1.70 – 1.62 (m, 1H, $C_{17}H_a$), 1.62 – 1.54 (m, 2H, β-N_3), 1.53 – 1.38 (m, 5H, $C_{16}H$), 1.30 – 1.22 (m, 2H, $C_{15}H_a$, $C_{17}H_b$), 1.16 (d, *J* = 7.1 Hz, 3H, $C_{20}CH_3$), 1.05 – 0.98 (m, 1H, $C_{15}H_b$), 0.99 (d, *J* = 6.8 Hz, 3H, $C_{22}CH_3$), 0.89 (s, 9H, TBS), 0.84 (app. d, *J* = 5.8 Hz, 6H, $C_{14}CH_3$, $C_{16}CH_3$), 0.05 (s, 6H, TBS); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 215.1, 134.2, 132.2, 130.7, 118.5, 105.3, 75.5, 75.2, 64.9, 64.5, 51.5, 48.4, 47.0, 43.3, 39.3, 35.7, 33.1, 30.0, 29.8, 29.5, 26.6, 26.3, 25.5, 20.1, 18.6, 17.7, 15.2, 10.6, -3.9, -4.0; **HRMS**: Exact mass calcd for $C_{32}H_{59}N_3NaO_5Si$ $[M+Na]^+$: 616.4122; found 616.4099 (FAB+).



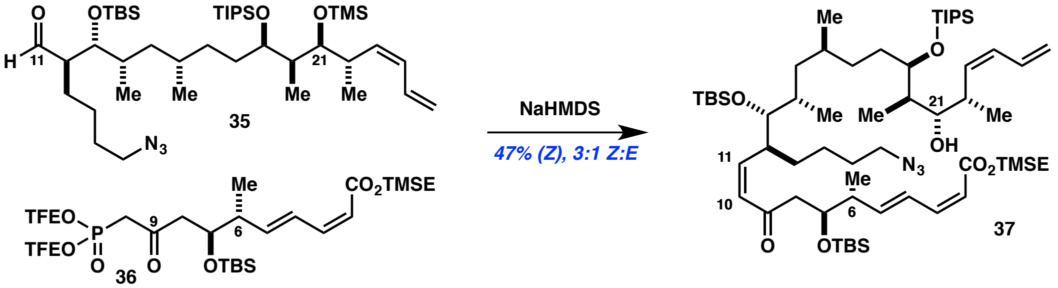
34

To a cooled (-78 °C) solution of keto-alcohol **33** (90 mg, 0.15 mmol, 1 equiv) in 1:1 THF / MeOH (3 mL, 0.05M) was added Et_2B-OMe (1M THF, 455 μL, 0.45 mmol, 3 equiv) dropwise. After 1h at -78 °C, $NaBH_4$ (11 mg, 0.30 mmol, 2 equiv) was added. After an additional 4h, the reaction mixture was quenched with AcOH (100 μL) and diluted with EtOAc (20 mL). Saturated aqueous $NaHCO_3$ (20 mL) was then added. The aqueous layer was separated and extracted with EtOAc (5x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude reaction mixture was azeotroped with methanol (3x20 mL) in order to hydrolyze the intermediate boronate. Purification was accomplished by silica gel flash column chromatography (10-20% EtOAc/Hex) affording *syn*-diol **34** (80 mg, 89% yield). **TLC** R_f = 0.30 (25% EtOAc/Hex); $[\alpha]^{22}_D$ -6.7 (*c* = 0.5, CH_2Cl_2); **IR** (thin film) 3420 (bs), 2927, 2856, 2095, 1712, 1462, 1252, 1063, 836, 773 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.64 (dt, *J* = 16.9, 10.6 Hz, 1H, $C_{25}H$), 6.19 (t, *J* = 11.0 Hz, 1H, $C_{24}H$), 5.30 – 5.23 (m, 2H, $C_{23}H$, $C_{26}H_a$), 5.18 (d, *J* = 10.1 Hz, 1H, $C_{26}H_b$), 4.84 (d, *J* = 4.0 Hz, 1H, $C_{11}H$), 3.97 – 3.88 (m, 2H), 3.83 – 3.75 (m, 3H, $C_{19}H$), 3.67 (dd, *J* = 5.8, 2.4 Hz, 1H, $C_{13}H$), 3.46 (dd, *J* = 9.2, 2.2 Hz, 1H, $C_{21}H$), 3.25 (t, *J* = 6.9 Hz, 2H, α-N_3), 2.86 – 2.76 (m, 1H, $C_{22}H$), 1.84 – 1.74 (m, 2H, $C_{12}H$, $C_{14}H$), 1.73 – 1.66 (m, 1H, $C_{20}H$), 1.63 - 1.55 (m, 2H, β-N_3), 1.54 – 1.37 (m, 8H, $C_{16}H$, $C_{17}H_a$, $C_{18}H_2$), 1.33 – 1.25 (m, 1H, $C_{15}H_a$), 1.04 – 0.92 (m, 2H, $C_{15}H_b$, $C_{17}H_b$), 0.94 (d, *J* = 7.1 Hz, 3H, $C_{20}CH_3$), 0.94 (d, *J* = 6.6 Hz, 3H, $C_{22}CH_3$), 0.89 (12H, TBS, $C_{16}CH_3$), 0.85 (d, *J* = 6.8 Hz, 3H, $C_{14}CH_3$), 0.05 (s, 3H, TBS), 0.04 (s, 3H, TBS); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.6, 132.1 (2C), 119.1, 105.3, 80.8, 77.2, 75.7, 64.9, 64.5, 51.5, 46.9, 43.4, 37.3, 36.5, 33.3, 33.0, 32.4, 30.3, 29.5, 26.6, 26.3, 25.5, 20.4, 18.6, 16.8, 15.3, 4.4, -3.9, -3.9; **HRMS**: Exact mass calcd for $C_{32}H_{61}N_3NaO_5Si$ $[M+Na]^+$: 618.4278; found 618.4263 (FAB+).

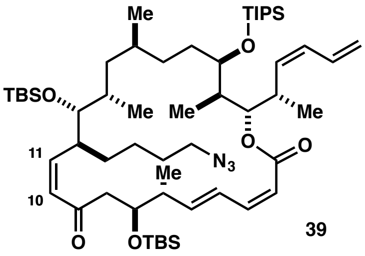


35

To a cooled (-78 °C) solution of *syn*-diol **34** (80 mg, 0.13 mmol, 1 equiv) in CH_2Cl_2 (2.7 mL, 0.05M) was added 2,6-lutidine (155 μL, 1.3 mmol, 10 equiv) and TIPS-OTf (40 μL, 0.15 mmol, 1.1 equiv). After 2h, freshly distilled TMS-OTf (121 μL, 0.67 mmol, 5 equiv) was added, and the reaction mixture was warmed to 0 °C. After 3h at 0 °C, the reaction mixture was quenched with water (5 mL). After vigorously stirring for 16h, the aqueous layer was separated and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (1-5% EtOAc/Hex) affording aldehyde **35** (73 mg, 70% yield). **TLC** R_f = 0.61 (10% EtOAc/Hex); $[\alpha]^{21}_D$ -8.2 (c = 1.0, CH_2Cl_2); **IR** (thin film) 2931, 2865, 2096, 1721, 1462, 1255, 1095, 836, 775, 676 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.72 (d, J = 3.2 Hz, 1H, $C_{11}H$), 6.55 (dt, J = 16.8, 10.6 Hz, 1H, $C_{25}H$), 5.99 (t, J = 11.0 Hz, 1H, $C_{24}H$), 5.55 (t, J = 10.6 Hz, 1H, $C_{23}H$), 5.15 (dd, J = 16.8, 2.0 Hz, 1H, $C_{26}H_a$), 5.06 (d, J = 10.1 Hz, 1H, $C_{26}H_b$), 3.84 (dd, J = 6.4, 3.4 Hz, 1H, $C_{19}H$), 3.76 – 3.67 (m, 2H, $C_{13}H$, $C_{21}H$), 3.26 (t, J = 6.9 Hz, 2H, α-N_3), 3.01 – 2.90 (m, 1H, $C_{22}H$), 2.40- 2.31 (m, 1H, $C_{12}H$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 204.7, 134.4, 132.7, 128.8, 117.1, 78.6, 77.6, 73.0, 55.8, 51.3, 41.1, 40.6, 35.6, 34.8, 33.0, 31.1, 30.7, 29.1, 27.2, 26.1, 24.9, 20.5, 19.5, 18.5, 18.5, 18.5, 15.4, 13.4, 9.6, 1.2, -3.7, -4.0; **HRMS:** Exact mass calcd for $C_{42}H_{85}N_3NaO_4Si_3$ $[M+Na]^+$: 802.5746; found 802.5753 (TOF MS ES+).



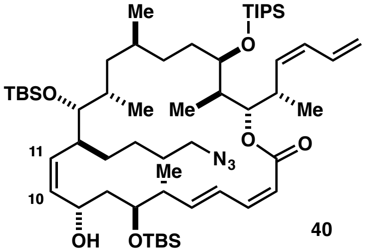
To a cooled (-78 °C) solution of phosphonate **36** (100 mg, 0.15 mmol, 4 equiv) in dry THF (300 μL) was added NaHMDS (1M THF, 146 μL, 0.15 mmol, 3.8 equiv). After 20 min, a solution of aldehyde **35** (30 mg, 38 μmol, 1 equiv) in THF (200 μL) was added, and the dark red reaction mixture was allowed to warm to room temperature. After 5 days, the reaction mixture was quenched at 0 °C with a solution of PPTS (5 mg) in MeOH (2 mL) in order to deprotect the C21 TMS ether. After 4h, the reaction mixture was diluted with pH 7.0 buffer solution (10 mL). The aqueous layer was separated and extracted with EtOAc (5x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (4-10% EtOAc/Hex) affording 20 mg of (Z)-enone **37** (47% yield) and an inseparable 23 mg mixture of (E)-enone **37** and unreacted aldehyde **35** (without its C21 TMS ether). The Z:E ratio was calculated to be *ca.* 3:1 based on analysis of the crude ^{1}H NMR. **TLC** R_f = 0.56 (10% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 (dd, J = 15.5, 11.3 Hz, 1H, C_4H), 6.64 (dt, J = 16.8, 10.6 Hz, 1H, $C_{25}H$), 6.54 (t, J = 11.3 Hz, 1H, C_3H), 6.21 (dd, J = 11.6, 9.9 Hz, 1H, $C_{11}H$), 6.15 – 6.05 (m, 2H, $C_{10}H$, $C_{24}H$), 6.02 (dd, J = 15.5, 8.0 Hz, 1H, C_5H), 5.58 (d, J = 11.3 Hz, 1H, C_2H), 5.46 (t, J = 10.3 Hz, 1H, $C_{23}H$), 5.19 (d, J = 16.8 Hz, 1H, $C_{26}H_a$), 5.10 (d, J = 10.1 Hz, 1H, $C_{26}H_b$), 4.28 – 4.17 (m, 3H, C_7H, TMSE), 3.98 – 3.90 (m, 1H, $C_{19}H$), 3.67 – 3.58 (m, 2H, $C_{12}H$, $C_{13}H$), 3.55 (m, 1H, $C_{21}H$), 3.23 (t, J = 6.9 Hz, 2H, α-N_3), 2.86 – 2.73 (m, 2H, $C_{22}H$, OH), 2.59 – 2.41 (m, 3H, C_8H_2, C_6H); **HRMS**: Exact mass calcd for $C_{61}H_{117}N_3NaO_7Si_4$ $[M+Na]^+$: 1138.7866; found 1138.7848 (TOF MS ES+).



39

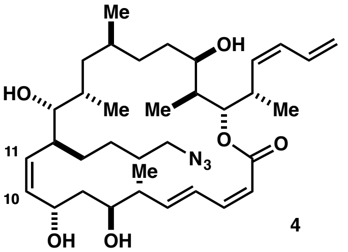
C1 Deprotection: To a cooled (0 °C) solution of TMSE ester **37** (20 mg, 0.018 mmol, 1 equiv) in DMF (1.3 mL) was added a solution of TAS-F (5 mg, 0.019, 1.05 equiv) in DMF (0.5 mL; final concentration 0.01 M) dropwise. The reaction mixture was allowed to warm to room temperature. After 24h, the reaction mixture was diluted with Et_2O (20 mL) and quenched at 0 °C with 1M $NaHSO_4$ (10 mL). The reaction mixture was further diluted with saturated aqueous NaCl (20 mL) and extracted with Et_2O (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford acid **38**, which was used immediately without purification.

Macrolactonization: To a solution of crude acid **38** in Toluene (18 mL, 0.001M) was added 2-methyl-6-nitrobenzoic anhydride (19 mg, 0.054 mmol, 3 equiv), DMAP (2 mg, 0.018 mmol, 1 equiv), and NEt_3 (25 µL, 0.18 mmol, 10 equiv). After 24h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) The aqueous layer was separated and extracted with EtOAc (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (1-5% EtOAc/Hex) affording macrocycle **39** (10 mg, 56% yield over 2 steps). **TLC** R_f = 0.67 (10% EtOAc/Hex); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.15 (dd, J = 15.4, 11.0 Hz, 1H, C_4H), 6.62 – 6.49 (m, 2H, $C_{25}H$, C_3H), 6.34 – 6.25 (m, 1H, $C_{11}H$), 6.22 – 6.13 (m, 1H, $C_{10}H$), 6.07 – 5.95 (m, 2H, $C_{24}H$, C_5H), 5.60 (d, J = 11.6 Hz, 1H, C_2H), 5.48 (t, J = 10.5 Hz, 1H, $C_{23}H$), 5.34 (dd, J = 9.0, 3.2 Hz, 1H, $C_{21}H$), 5.20 (d, J = 17.0 Hz, 1H, $C_{26}H_a$), 5.12 (d, J = 10.3 Hz, 1H, $C_{26}H_b$), 4.15 – 4.05 (m, 1H, C_7H), 3.83 (bs, 1H, $C_{19}H$), 3.64 (bs, 1H, $C_{12}H$), 3.42 (app. d, J = 4.1 Hz, 1H, $C_{13}H$), 3.23 (t, J = 6.9 Hz, 2H, α-N_3), 3.14 (bs, 1H, $C_{22}H$), 2.60 – 2.47 (m, 2H, C_8H_2), 2.45 – 2.36 (m, 1H, C_6H); ^{13}**C NMR** not included due to rotamers causing substantial line broadening.



40

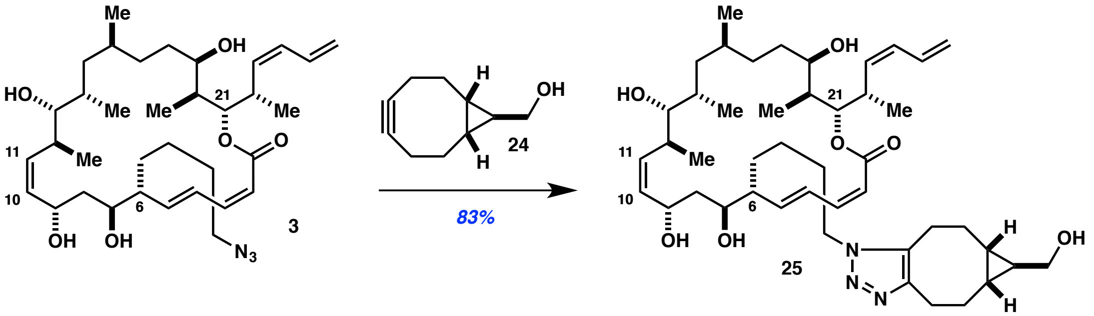
To a cooled (-78 °C) solution of enone **39** (10 mg, 10 µmol, 1 equiv) in Toluene (400 µL, 0.025M) was added (R)-2-Methyl-CBS oxazaborolidine (1M Tol, 40 µL, 40 µmol, 4 equiv) and catecholborane (50% w/w Toluene, 22 µL, 80 µmol, 8 equiv). After 20h at -78 °C, the reaction mixture was quenched with MeOH (2 mL), followed by saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was separated and extracted with EtOAc (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (5-10% EtOAc/Hex) affording **40** (8.0 mg, 80% yield). **TLC** R_f = 0.29 (10% EtOAc/Hex); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.10 – 7.01 (m, 1H, C_4H), 6.62 – 6.48 (m, 2H, $C_{25}H$, C_3H), 6.10 – 5.99 (m, 2H, $C_{24}H$, C_5H), 5.60 (d, J = 11.5 Hz, 1H, C_2H), 5.58 – 5.43 (m, 2H, $C_{11}H$, $C_{10}H$), 5.38 (t, J = 10.4 Hz, 1H, $C_{23}H$), 5.25 – 5.14 (m, 2H, $C_{26}H_a$, $C_{21}H$), 5.09 (d, J = 10.3 Hz, 1H, $C_{26}H_b$), 4.56 – 4.48 (m, 1H, C_9H), 4.15 – 4.07 (m, 1H, C_7H), 3.73 (bs, 1H, $C_{19}H$), 3.33 (bs, 1H, $C_{13}H$), 3.27 (t, J = 6.9 Hz, 1H, α-N_3), 3.06 (bs, 1H, $C_{22}H$), 2.59 (bs, 1H, $C_{12}H$), 2.48 (bs, 1H, C_6H), 1.86 (bs, 1H, $C_{20}H$); ^{13}**C NMR** not included due to rotamers causing substantial line broadening.



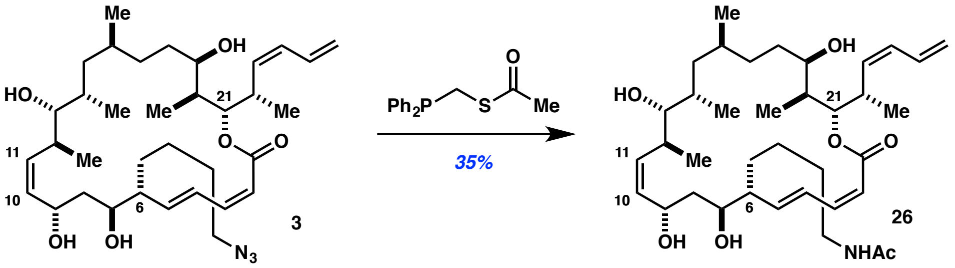
4

To a cooled (0 °C) solution of **40** (6.0 mg) in THF (1 mL) in a Nalgene tube was added HF-pyridine (100 µL). The reaction mixture was allowed to warm to room temperature. At t = 12h and 24h, additional HF-pyridine (50 µL; total of 200 µL) was added. After a total reaction time of 72h, the reaction mixture was slowly quenched at 0 °C with saturated aqueous $NaHCO_3$ (10 mL) and then diluted with CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (5x20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (20-50%

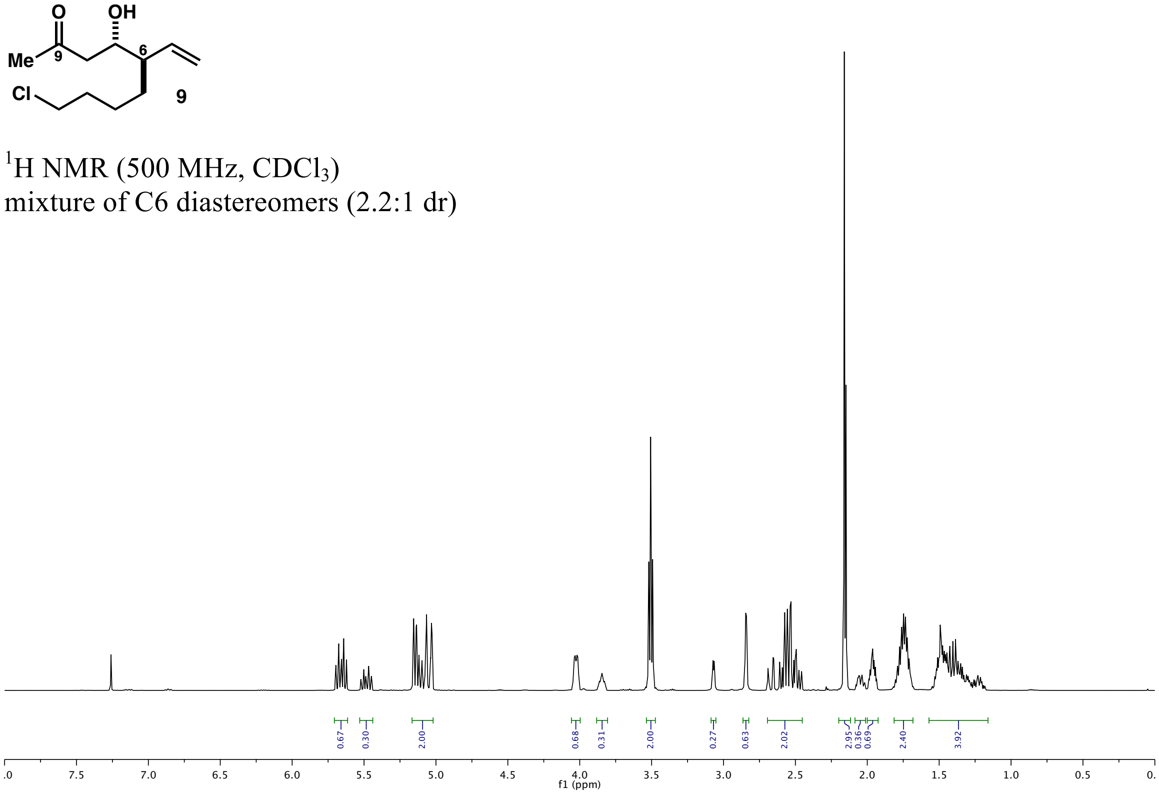
EtOAc/Hex) affording **4** (2.0 mg, 54% yield). **TLC** R_f = 0.53 (80% EtOAc/Hex); **$[\alpha]^{23}_D$** 62.1 (c = 0.1, CH_2Cl_2); **IR** (thin film) 3436 (bs), 2927, 2096, 1694, 1404, 1278, 1182, 1062, 963 cm^{-1}; **^{1}H NMR** (500 MHz, MeOD) δ 7.17 (dd, J = 15.6, 11.2 Hz, 1H, C_4H), 6.73 – 6.59 (m, 2H, $C_{25}H$, C_3H), 6.14 (dd, J = 15.6, 6.9 Hz, 1H, C_5H), 6.03 (t, J = 11.1 Hz, 1H, $C_{24}H$), 5.53 (d, J = 11.4 Hz, 1H, C_2H), 5.51 – 5.41 (m, 2H, $C_{11}H$, $C_{10}H$), 5.32 (t, J = 10.6 Hz, 1H, $C_{23}H$), 5.22 (d, J = 16.6 Hz, 1H, $C_{26}H_a$), 5.15 – 5.08 (m, 2H,$C_{26}H_b$, $C_{21}H$), 4.63 – 4.56 (m, 1H, C_9H), 4.04 – 3.99 (m, 1H, C_7H), 3.23 (dd, J = 7.5, 3.0 Hz, 1H, $C_{13}H$), 3.16 – 3.11 (m, 1H, $C_{22}H$), 2.55 (m, 2H, $C_{12}H$, C_6H), 1.12 (d, J = 6.9 Hz, 3H, C_6CH_3), 1.03 (d, J = 6.8 Hz, 3H, $C_{20}CH_3$), 0.99 (d, J = 6.7 Hz, 3H, $C_{22}CH_3$); **HRMS**: Exact mass calcd for $C_{35}H_{57}N_3NaO_6$ $[M+Na]^+$: 638.4145; found 638.4146 (TOF MS ES+).



To a solution of **3** (1.0 mg, 1.6 μmol, 1 equiv) in 1:2 CD_3CN/D_2O (0.5 mL) was added cyclo-octyne **24** (2.0 mg, 13 μmol, 8 equiv). After 72h, the reaction was directly purified by silica gel flash column chromatography (100% EtOAc to elute cyclooctyne, then 10-15% $MeOH/CH_2Cl_2$ to elute product) affording triazole **25** (1.0 mg, 1:1 dr, 83% yield). **TLC** R_f = 0.42 (10% $MeOH/CH_2Cl_2$); **IR** (thin film) 3385 (bs), 2925, 1699, 1638, 1458, 1383, 1066, 732 cm^{-1}; **^{1}H NMR** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, J = 16.0, 11.4 Hz, 1H, C_4H), 6.59 (dt, J = 16.9, 10.7 Hz, 1H, $C_{25}H$), 6.50 – 6.44 (m, 1H, C_3H), 6.02 – 5.94 (m, 2H, C_5H, $C_{24}H$), 5.56 (t, J = 10.3 Hz, 1H, $C_{10}H$), 5.49 (d, J = 11.3 Hz, 1H, C_2H), 5.32 (t, J = 10.5 Hz, 1H, $C_{11}H$), 5.26 (t, J = 10.5 Hz, 1H, $C_{23}H$), 5.17 (dd, J = 16.8, 2.0 Hz, 1H, $C_{26}H_a$), 5.09 (d, J = 10.2 Hz, 1H, $C_{26}H_b$), 4.93 (dd, J = 8.4, 2.5 Hz, 1H, $C_{21}H$), 4.79 (dt, J = 10.0, 5.4 Hz, 1H, C_9H), 4.26 – 4.17 (m, 2H, α-triazole), 3.99 – 3.90 (m, 1H, C_7H), 3.60 – 3.53 (m, 1H), 3.51 – 3.42 (m, 2H, $C_{19}H$), 3.27 (d, J = 7.9 Hz, 1H, $C_{13}H$), 3.09 (m, 1H), 3.04 – 2.94 (m, 1H, $C_{22}H$), 2.90 – 2.80 (m, 2H), 2.79 – 2.71 (m, 1H, $C_{12}H$), 2.69 – 2.61 (m, 1H), 2.48 – 2.36 (m, 2H), 2.25 – 2.18 (m, 1H, C_6H), 1.90 – 1.85 (m, 1H, $C_{20}H$); **HRMS**: Exact mass calcd for $C_{45}H_{72}N_3O_7$ $[M+H]^+$: 766.5370; found 766.5392 (FAB+).



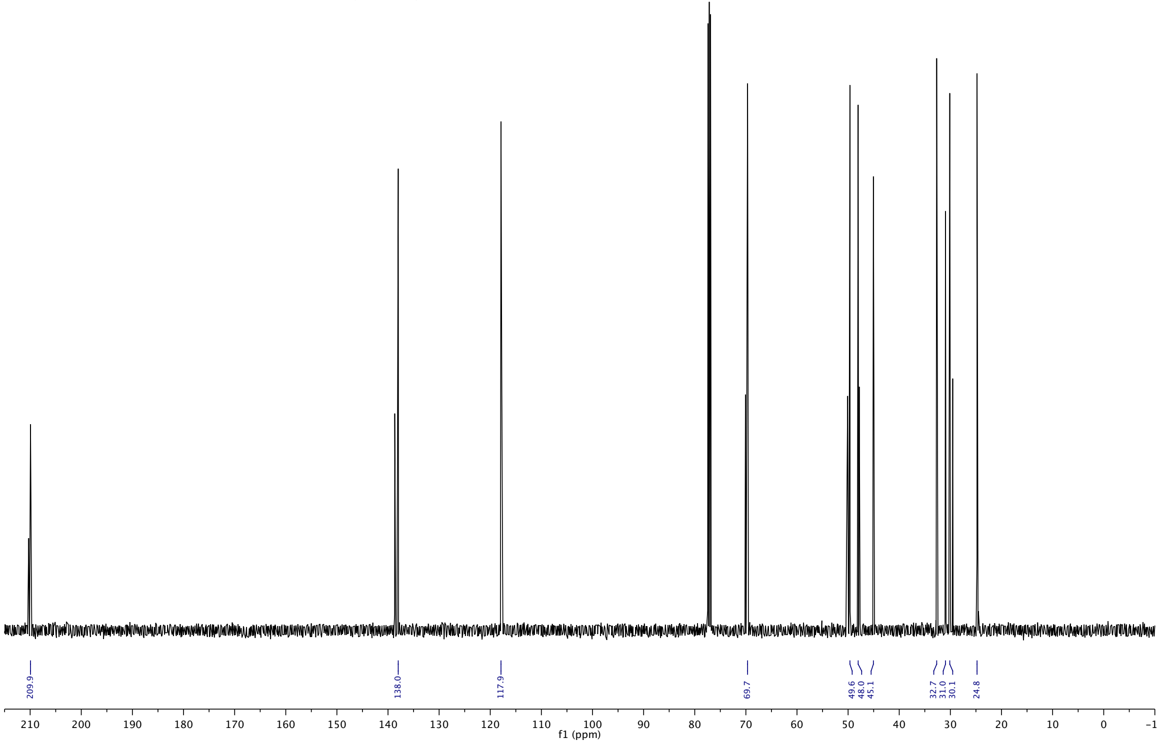
To a solution of **3** (3.4 mg, 5.5 μmol, 1 equiv) in 1:1 THF/H_2O (0.5 mL, degassed) was added the Raines ligation reagent (15 mg, 55 μmol, 10 equiv) under Argon. After 48h, the reaction was directly purified by silica gel flash column chromatography (100% EtOAc, then 10-20% $MeOH/CH_2Cl_2$) affording amide **26** (1.2 mg, 35% yield). **TLC** R_f = 0.5 (10% $MeOH/CH_2Cl_2$); **$[\alpha]^{19}_D$** 26.2 (c = 0.1, CH_2Cl_2); **IR** (thin film) 3358, 2923, 2854, 1696, 1638, 1460, 1440, 1274, 1174, 1120, 1064 cm^{-1}; **^{1}H NMR** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 – 6.55 (m, 1H, $C_{25}H$), 6.49 (t, J = 11.2 Hz, 1H, C_3H), 6.06 – 5.95 (m, 2H, C_5H, $C_{24}H$), 5.57 (t, J = 10.2 Hz, 1H, $C_{10}H$), 5.49 (d, J = 11.3 Hz, 1H, C_2H), 5.34 (t, J = 10.5 Hz, 1H, $C_{11}H$), 5.26 (t, J = 10.5 Hz, 1H, $C_{23}H$), 5.18 (d, J = 17.1 Hz, 1H, $C_{26}H_a$), 5.10 (d, J = 10.9 Hz, 1H, $C_{26}H_b$), 4.94 (dd, J = 8.4, 2.7 Hz, 1H, $C_{21}H$), 4.84 – 4.76 (m, 1H, C_9H), 4.03 – 3.96 (m, 1H, C_7H), 3.51 – 3.44 (m, 1H, $C_{19}H$), 3.33 – 3.18 (m, 3H, $C_{13}H$, α-amide), 3.04 – 2.95 (m, 1H, $C_{22}H$), 2.80 – 2.71 (m, 1H, $C_{12}H$), 1.97 (s, 3H, NHMe); **LRMS**: Exact mass calcd for $C_{37}H_{62}NO_7$ $[M+H]^+$: 632.45; found 632.40 (FAB+).

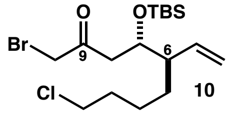


9

¹H NMR (500 MHz, $CDCl_3$)
mixture of C6 diastereomers (2.2:1 dr)

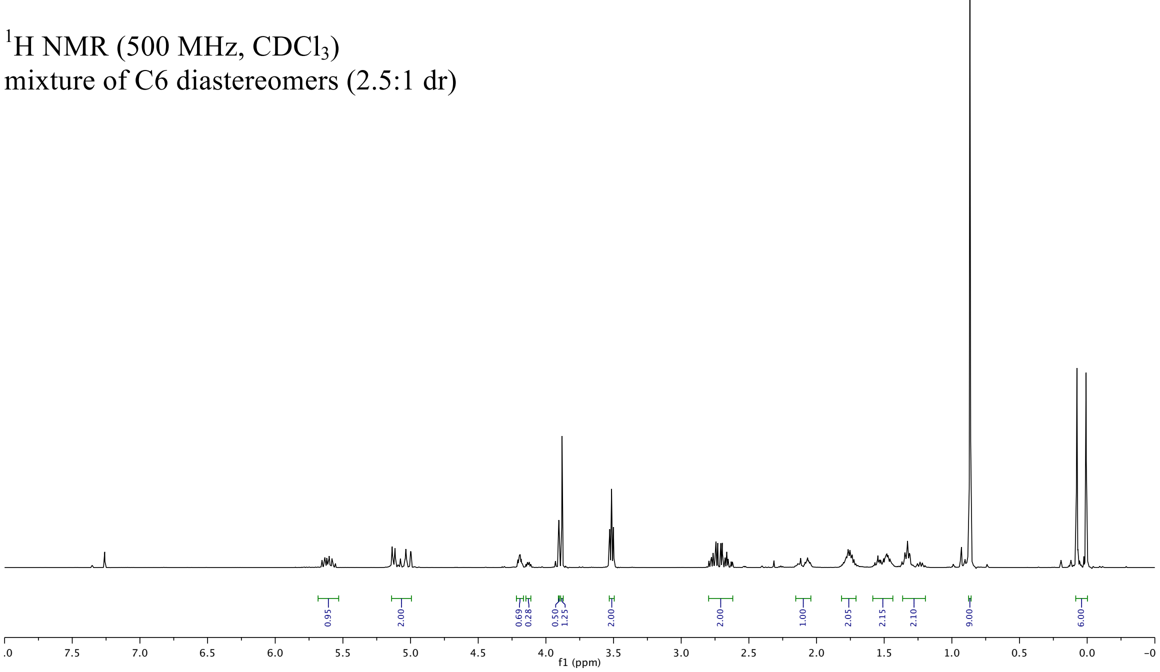
¹³C NMR (125 MHz, $CDCl_3$)
mixture of C6 diastereomers (2.2:1)



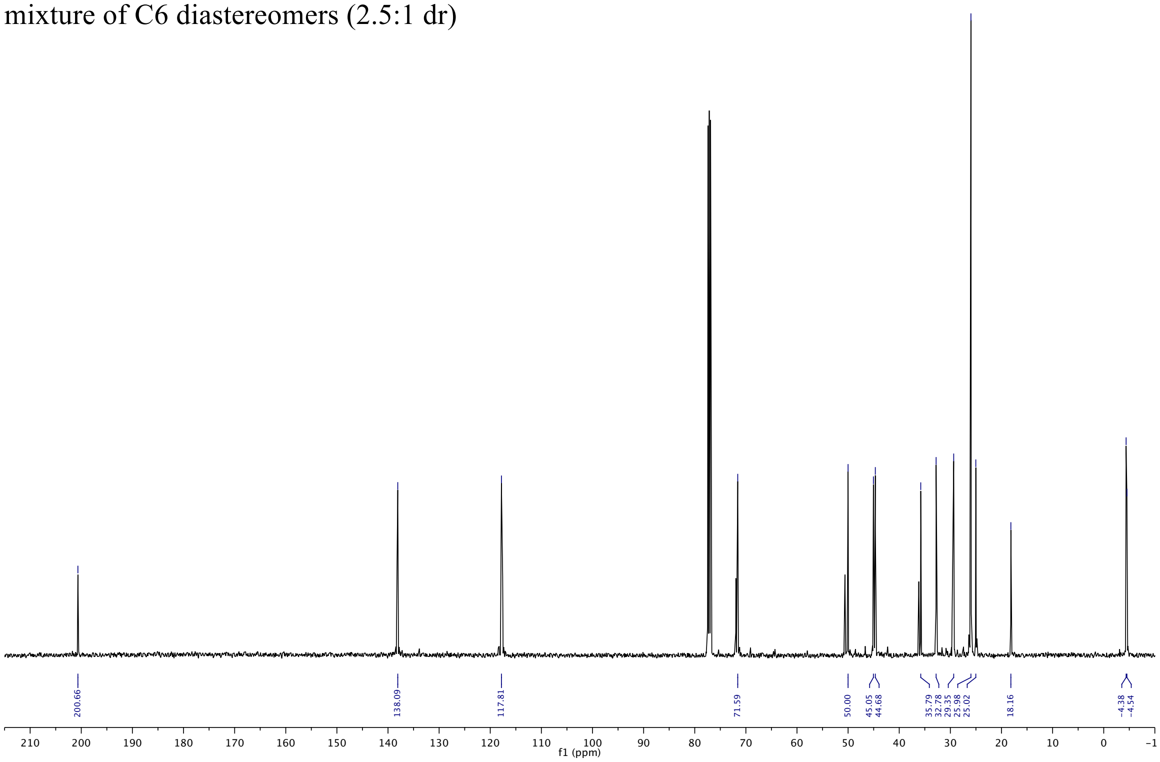


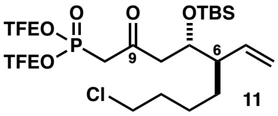
10

^{1}H NMR (500 MHz, $CDCl_3$)
mixture of C6 diastereomers (2.5:1 dr)



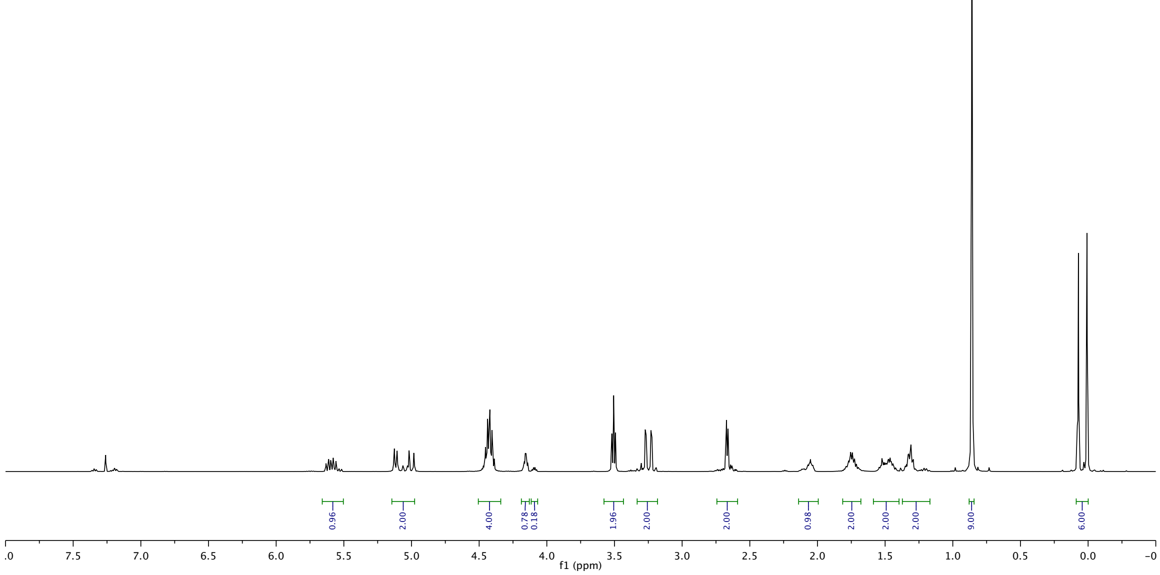
^{13}C NMR (125 MHz, $CDCl_3$)
mixture of C6 diastereomers (2.5:1 dr)



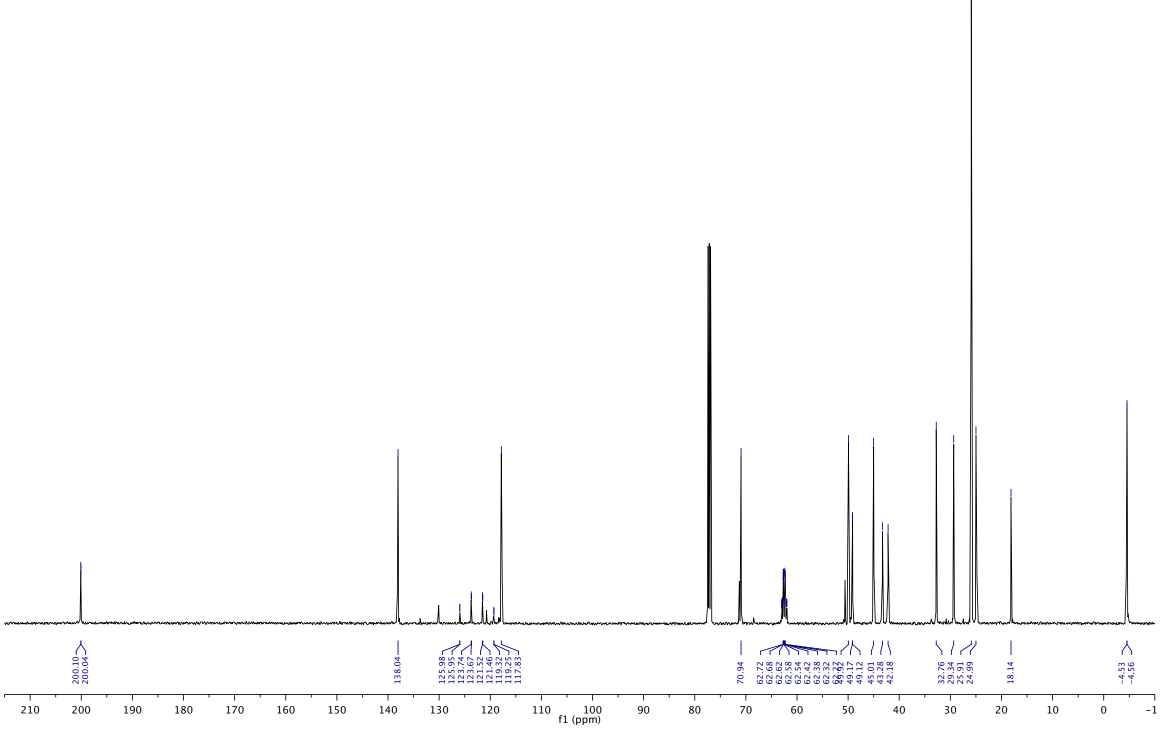


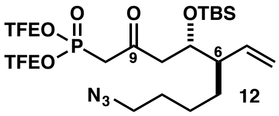
11

^{1}H NMR (500 MHz, $CDCl_3$)
mixture of C6 diastereomers (4.3:1 dr)



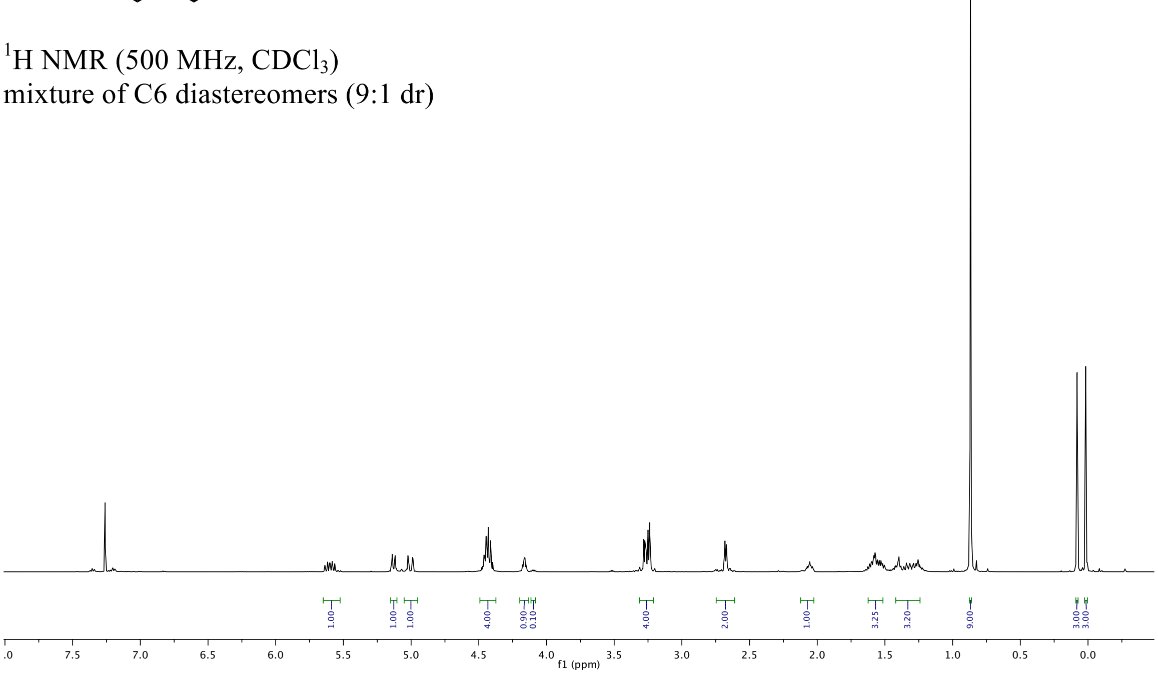
^{13}C NMR (125 MHz, $CDCl_3$)
mixture of C6 diastereomers (4.3:1 dr)



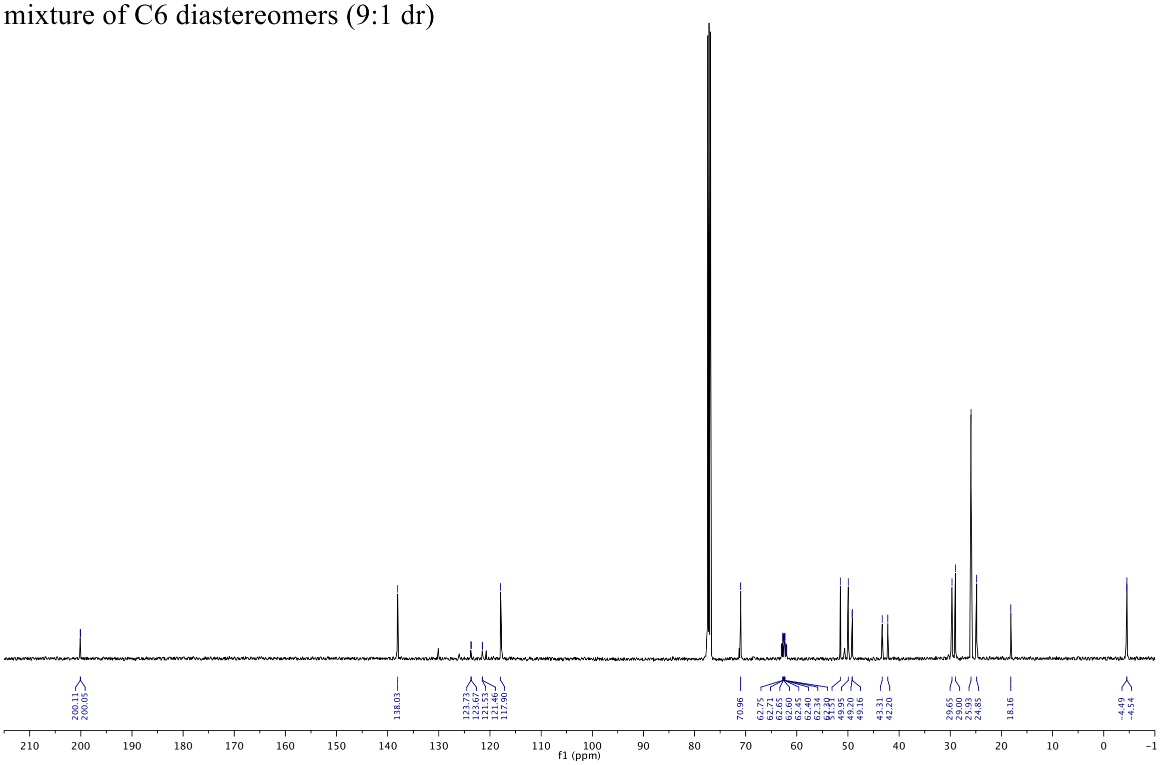


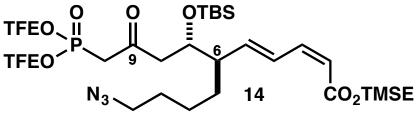
12

^{1}H NMR (500 MHz, CDCl$_3$)
mixture of C6 diastereomers (9:1 dr)



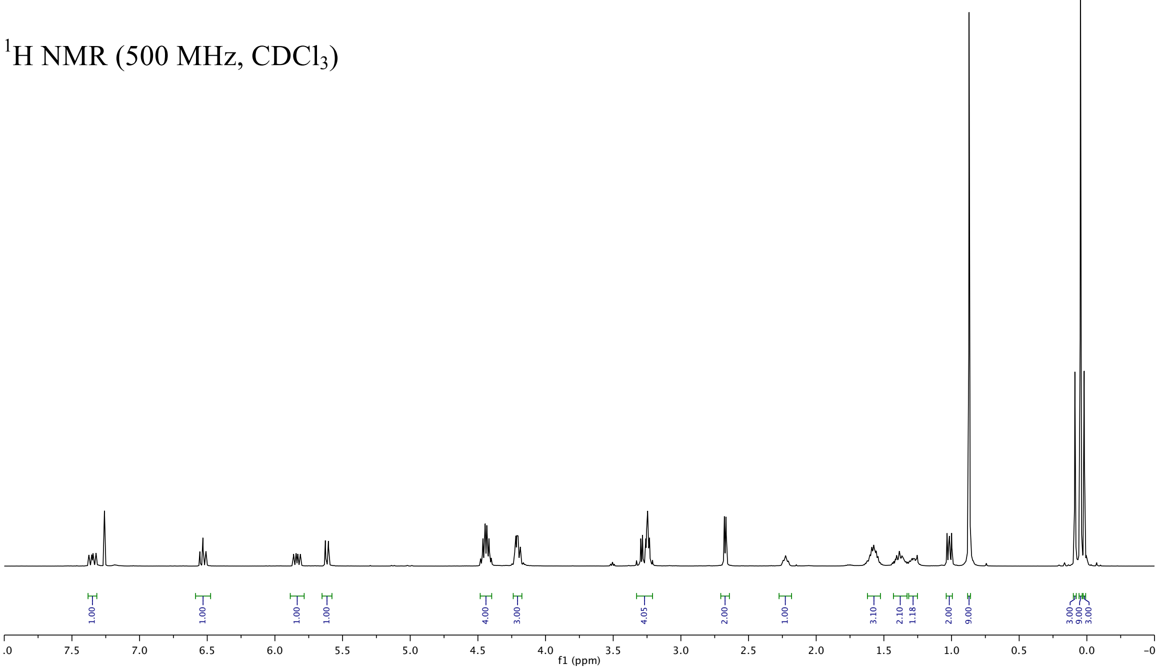
^{13}C NMR (125 MHz, CDCl$_3$)
mixture of C6 diastereomers (9:1 dr)



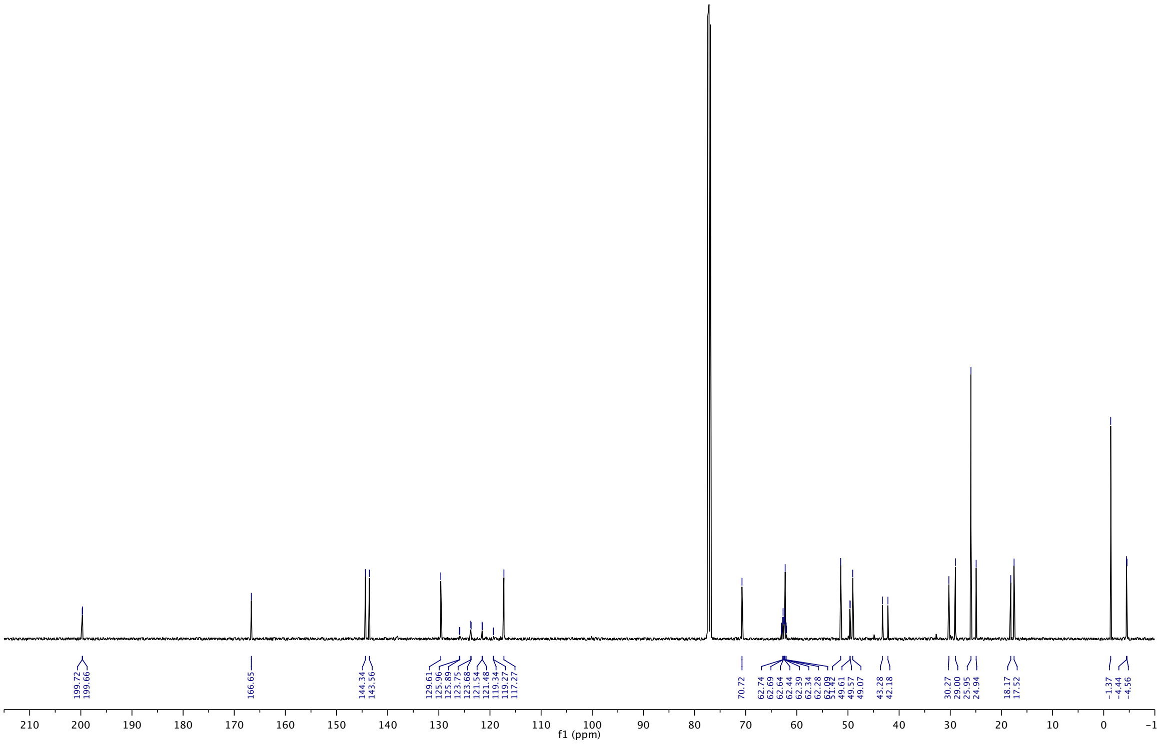


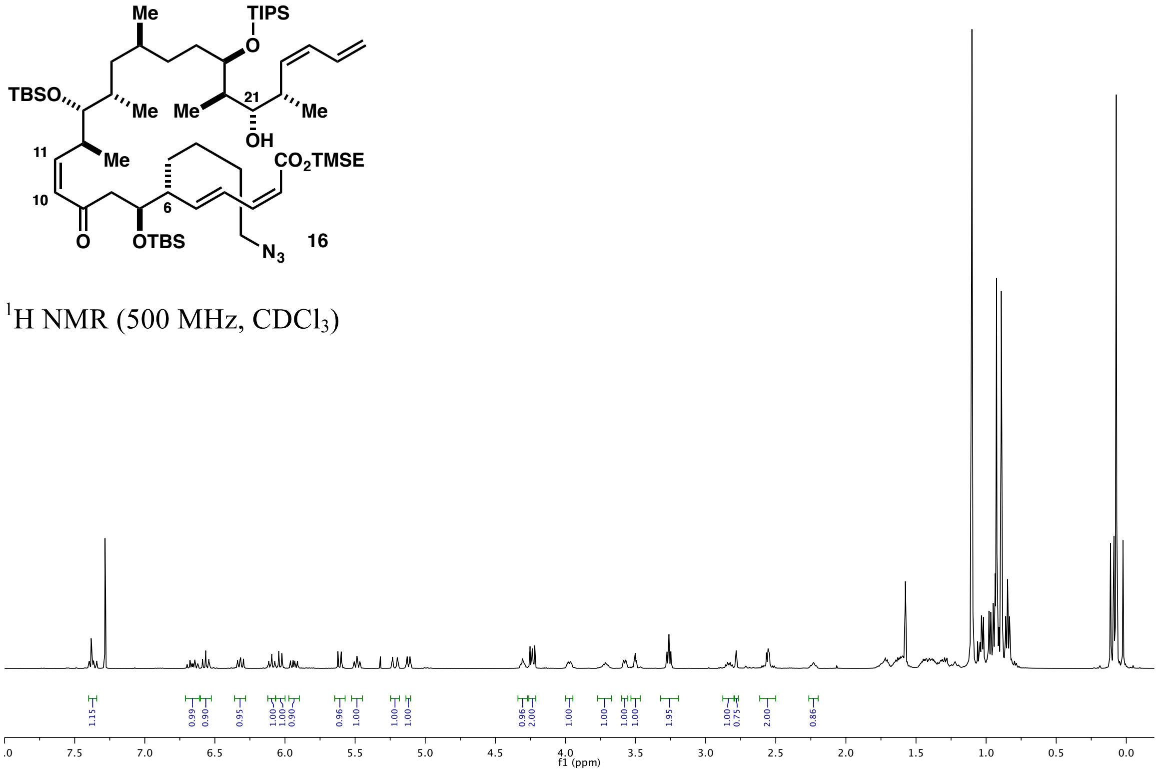
14

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

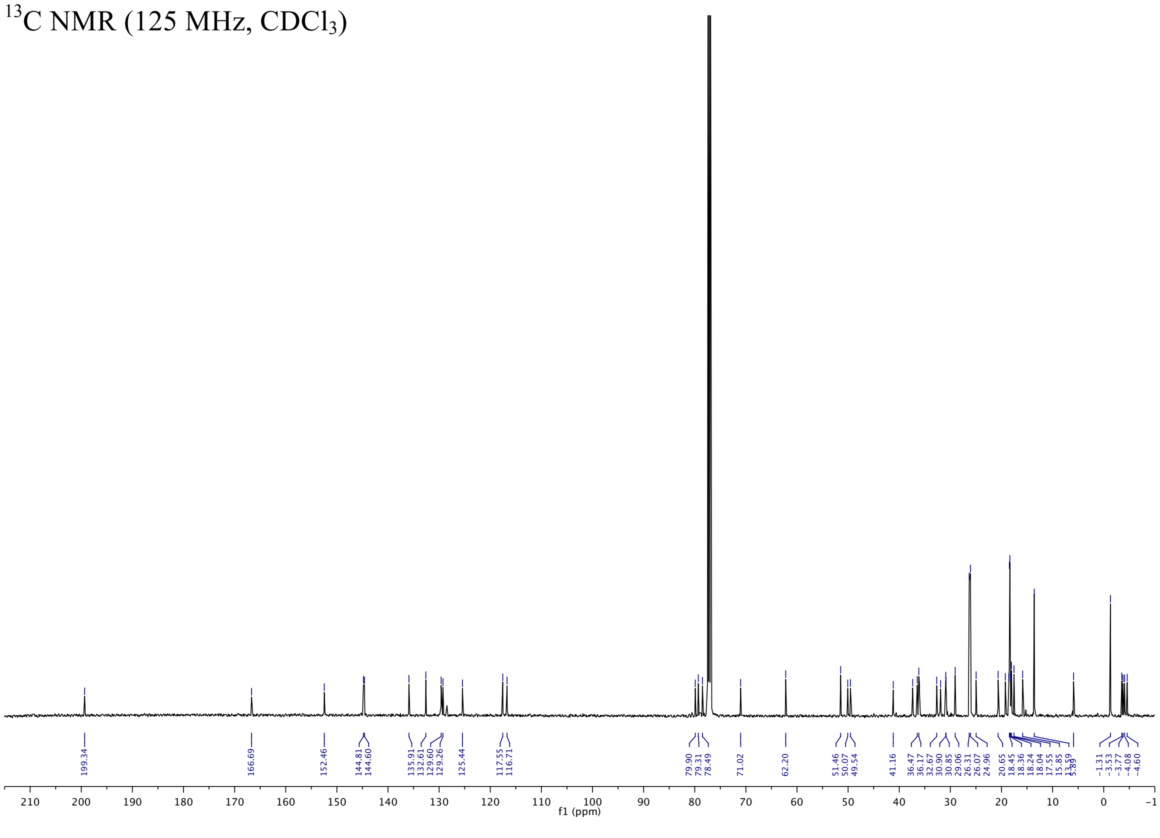


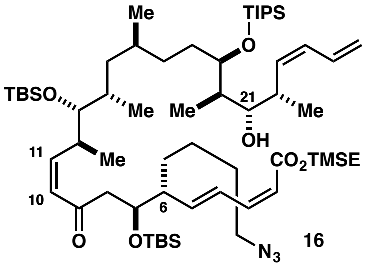


16

^{1}H NMR (500 MHz, $CDCl_3$)

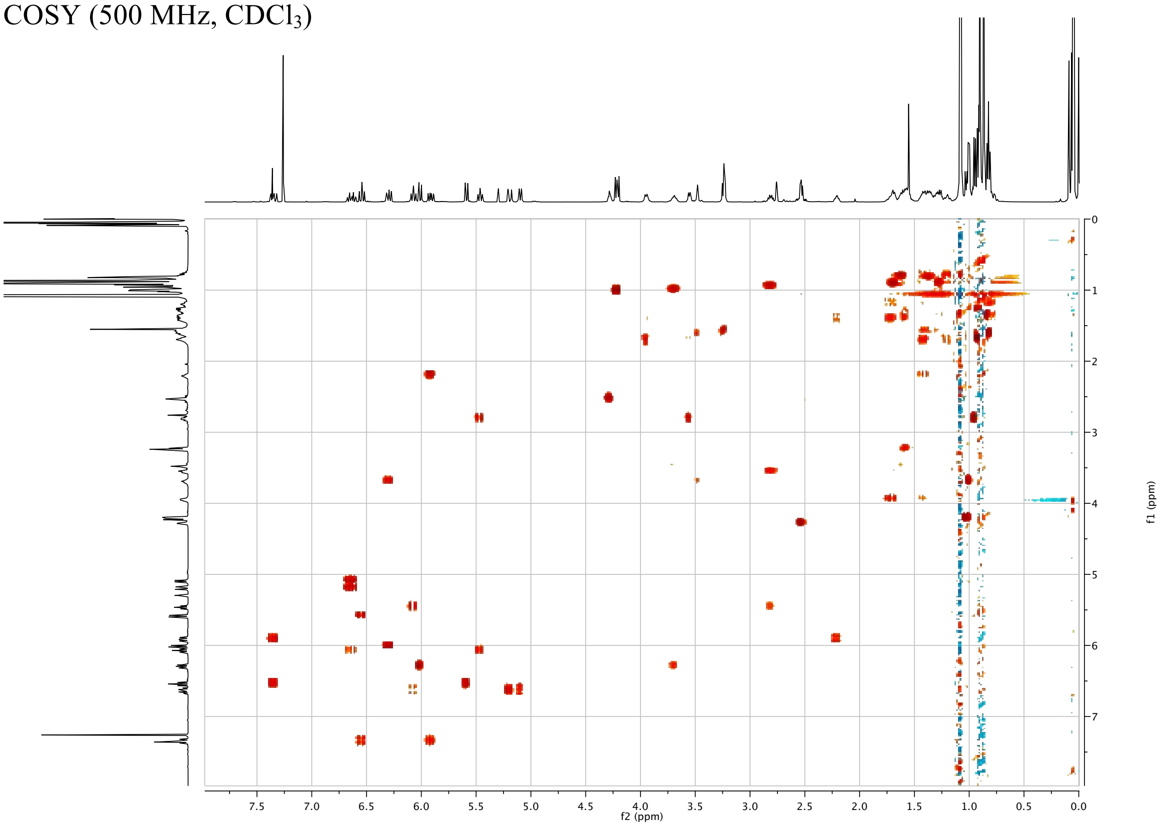
^{13}C NMR (125 MHz, $CDCl_3$)

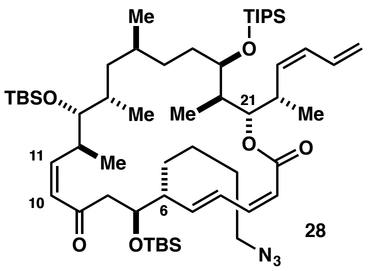




16

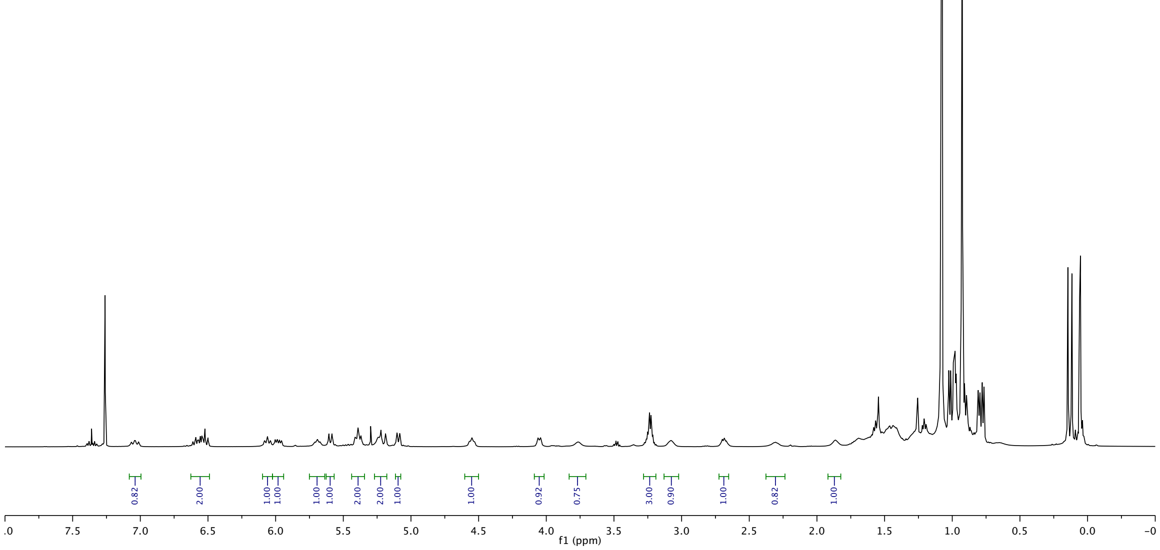
COSY (500 MHz, $CDCl_3$)

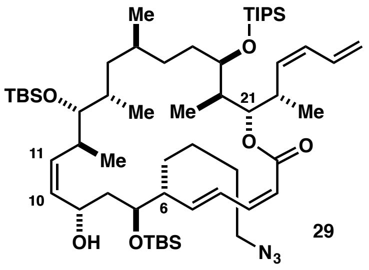




28

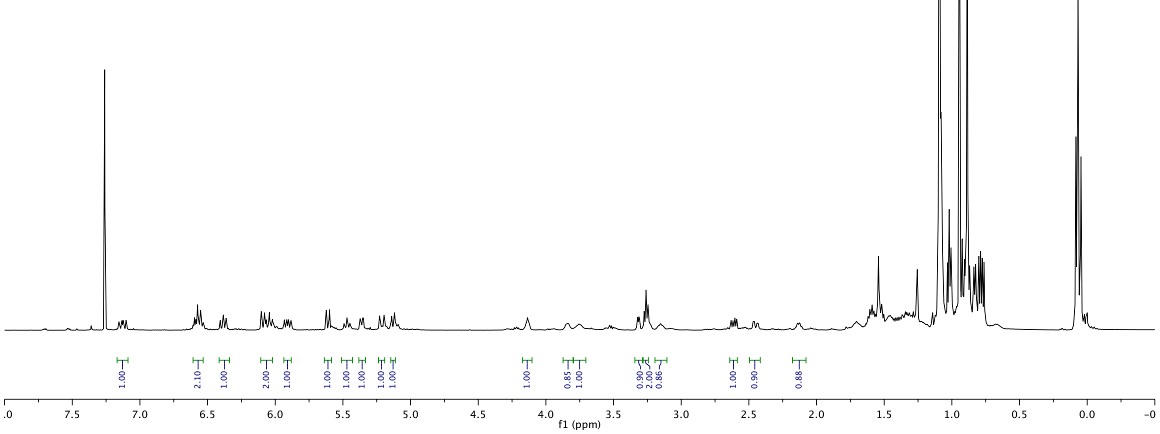
^{1}H NMR (500 MHz, CDCl$_3$)

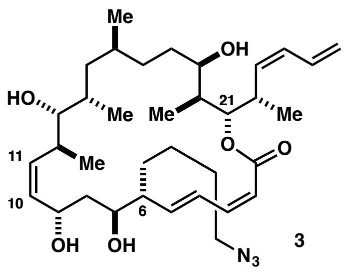




29

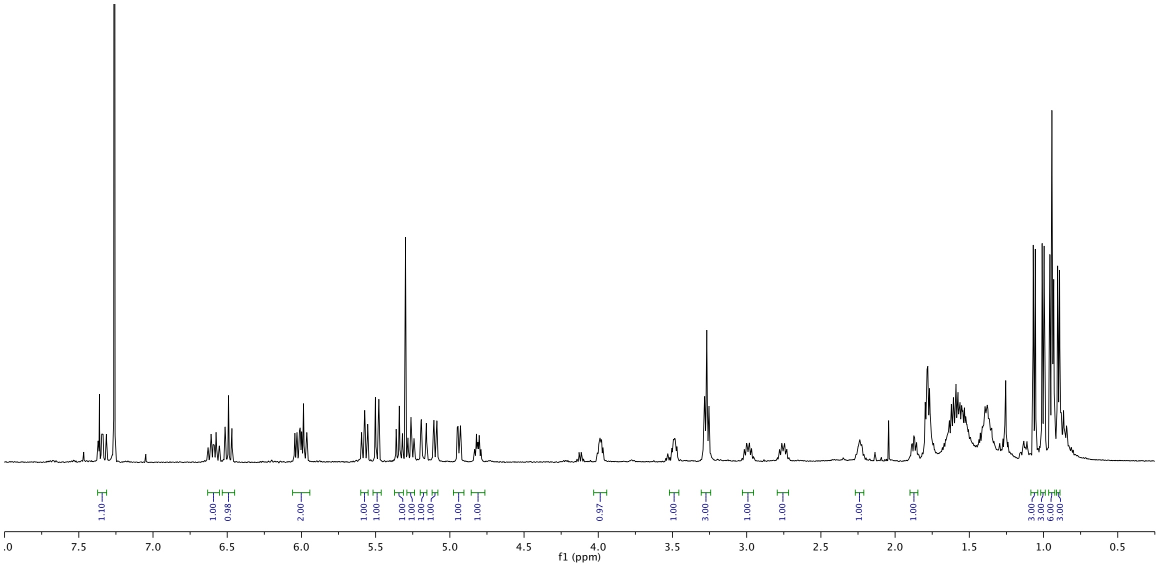
^{1}H NMR (500 MHz, CDCl$_3$)



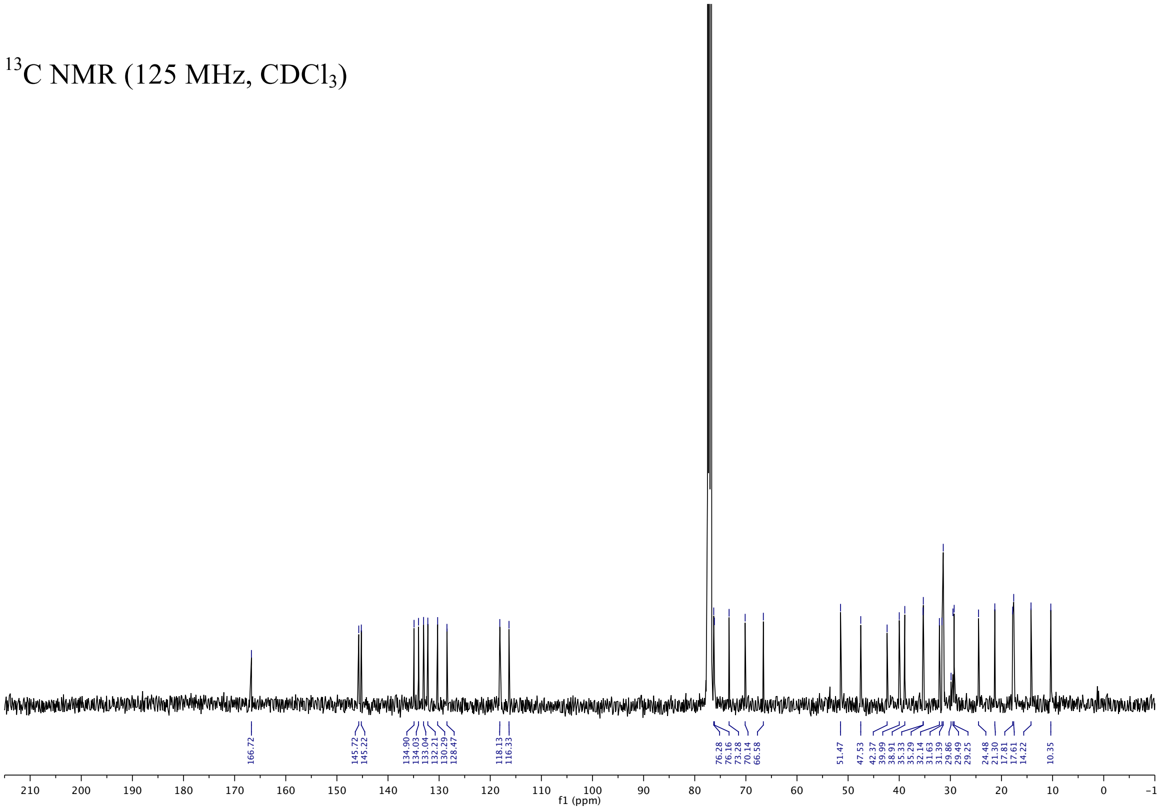


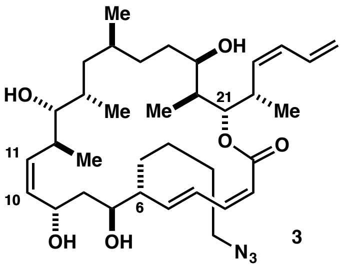
3

^{1}H NMR (500 MHz, CDCl$_3$)



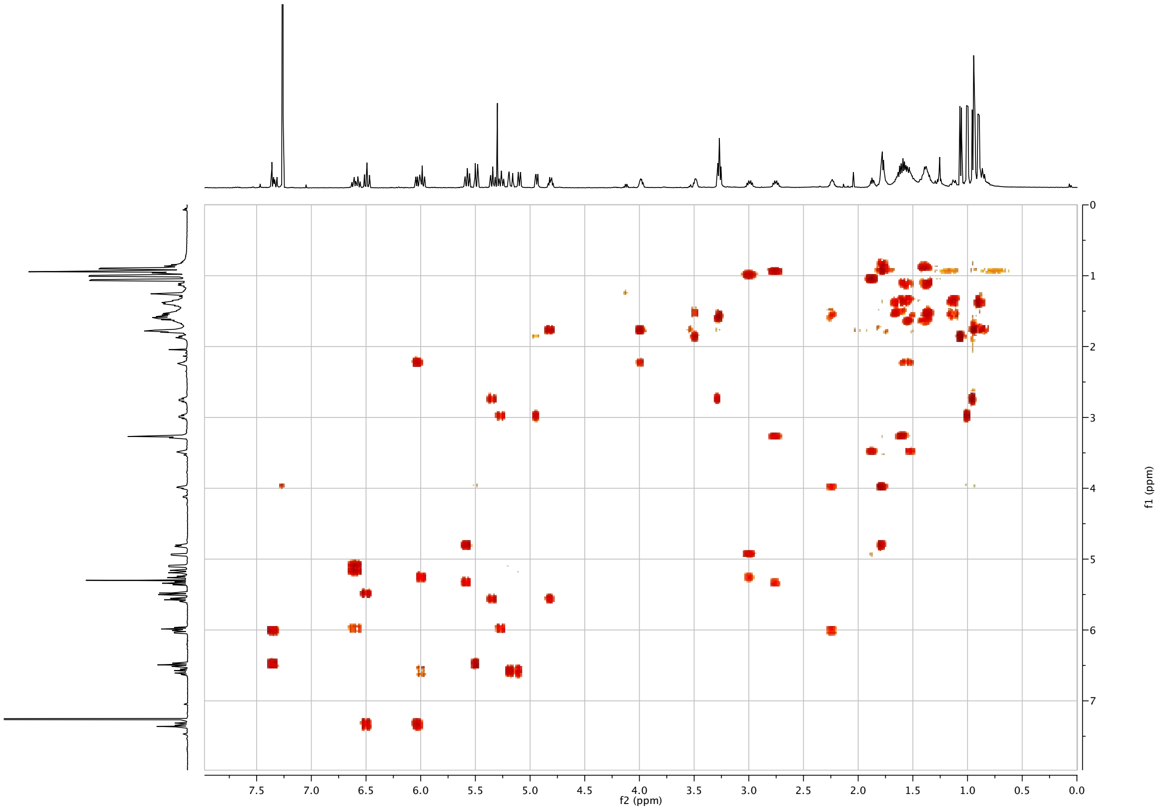
^{13}C NMR (125 MHz, CDCl$_3$)



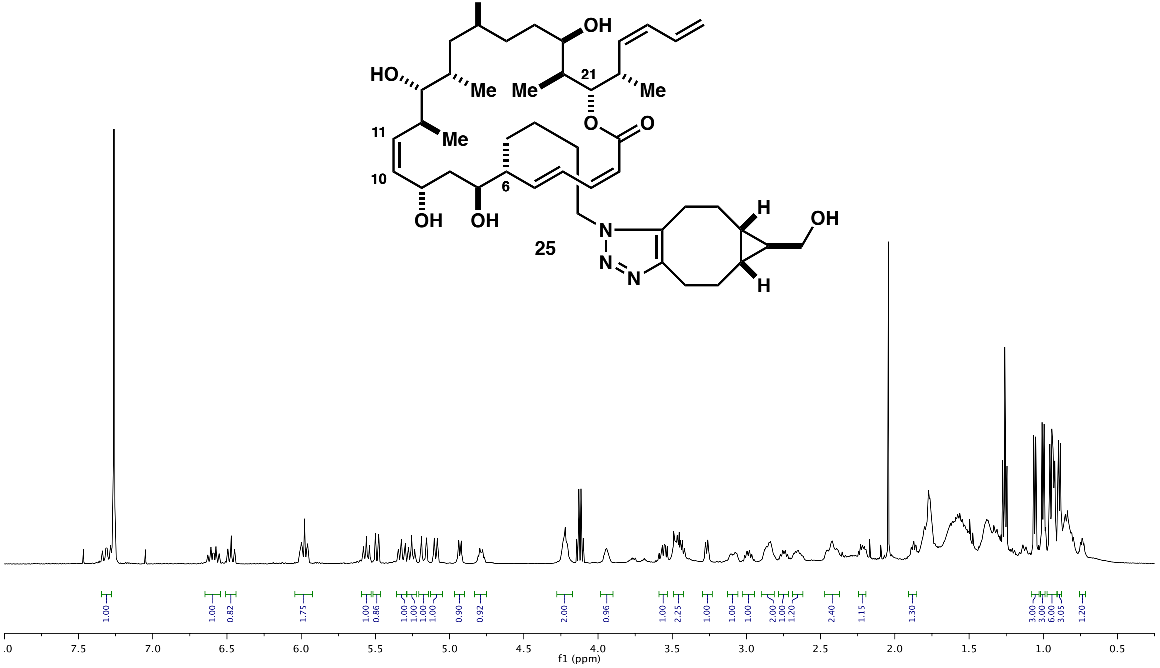


3

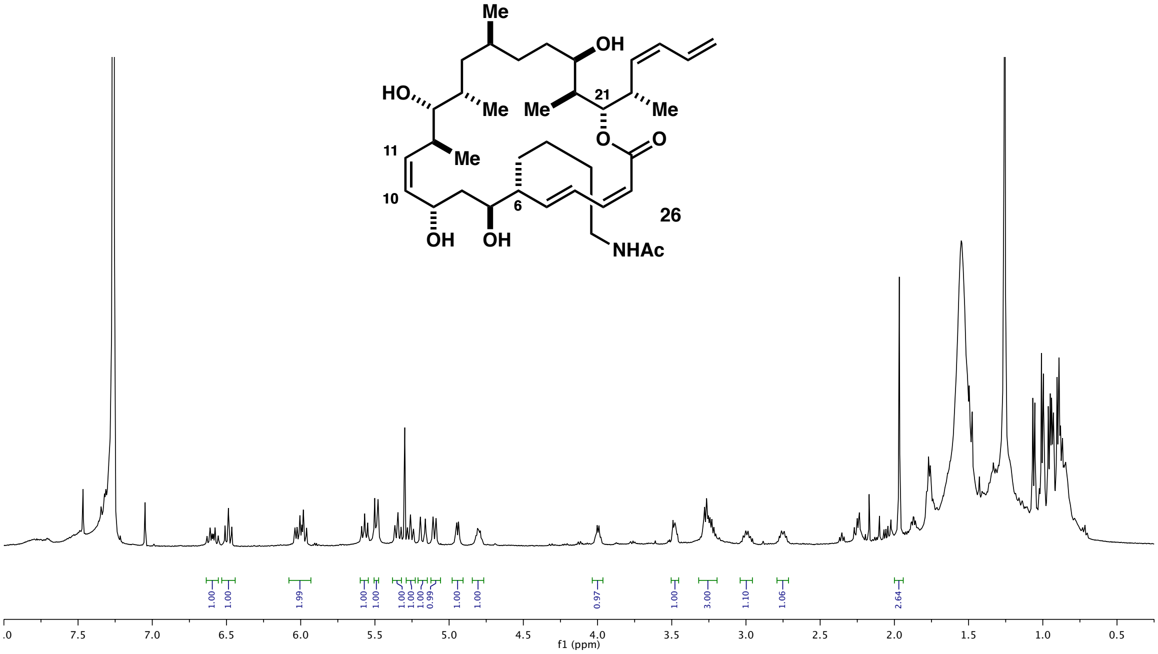
COSY (500 MHz, $CDCl_3$)

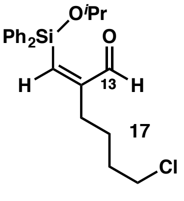


^{1}H NMR (500 MHz, $CDCl_3$)

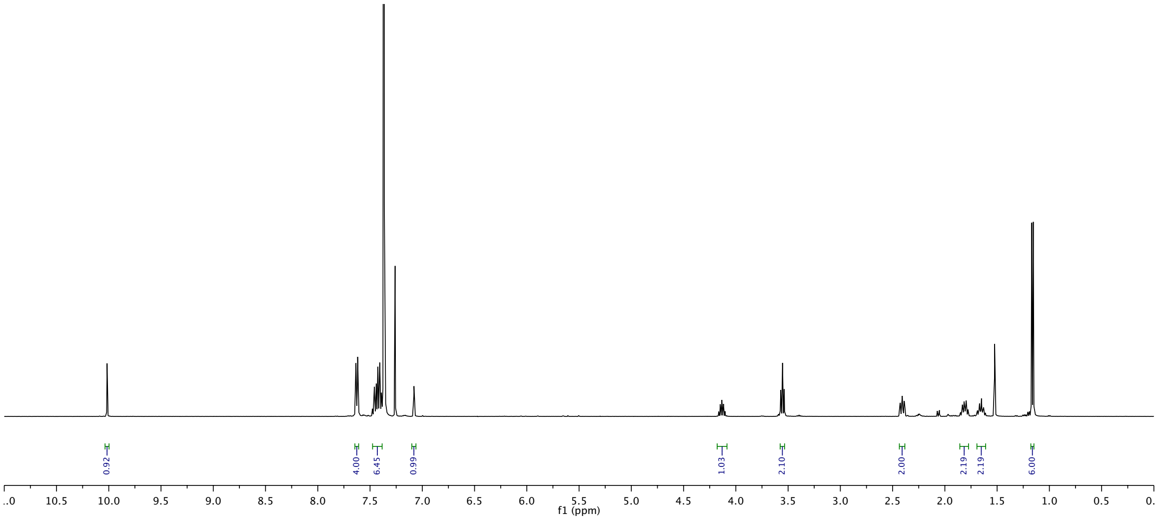


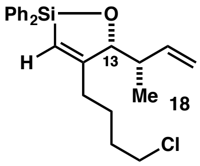
^{1}H NMR (500 MHz, $CDCl_3$)





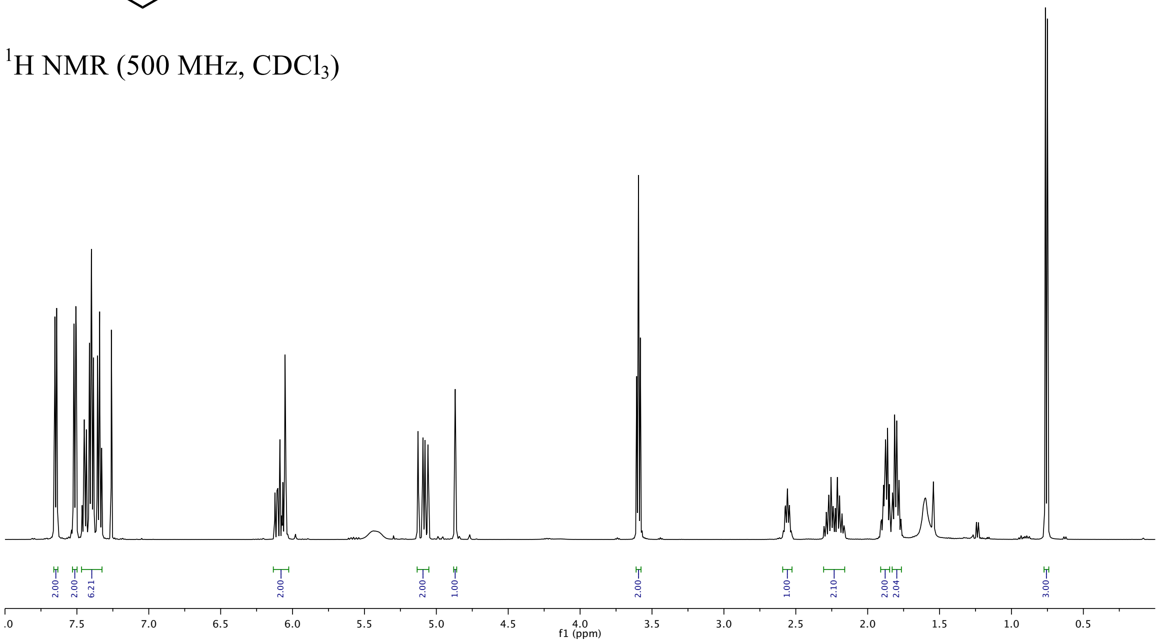
aliquot ^{1}H NMR (400 MHz, CDCl3) of the crude silylformylation reaction mixture



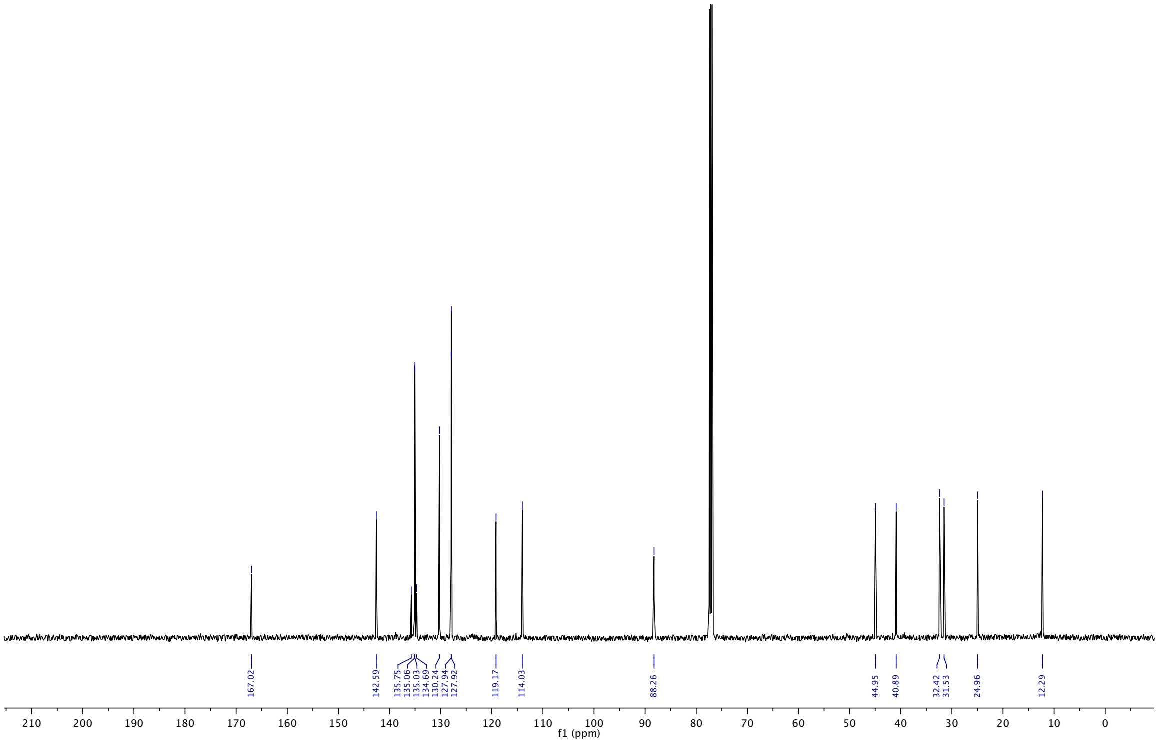


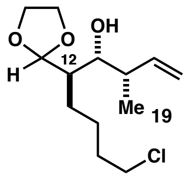
18

^{1}H NMR (500 MHz, CDCl$_3$)

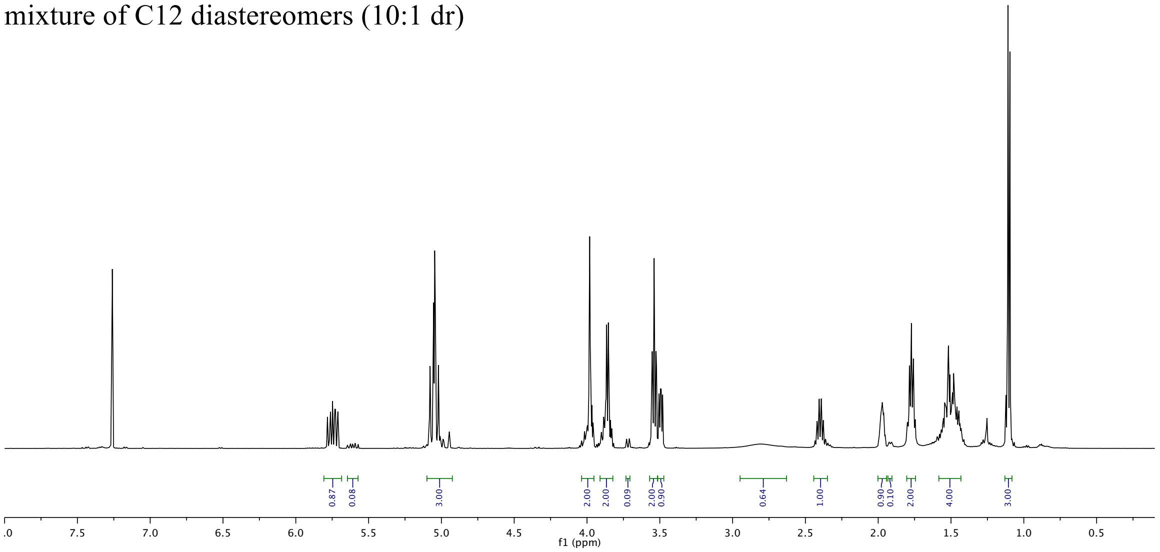


^{13}C NMR (125 MHz, CDCl$_3$)

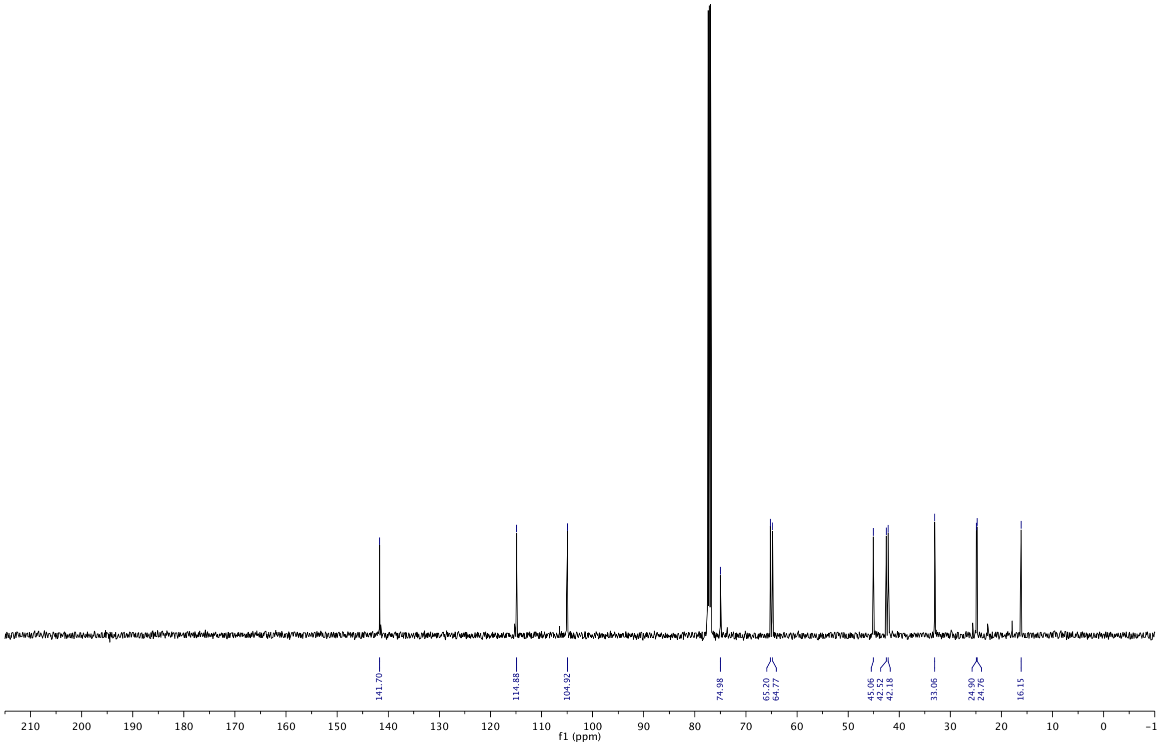


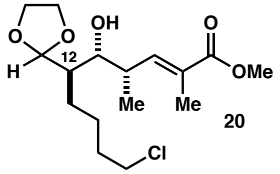


^{1}H NMR (500 MHz, CDCl$_3$)
mixture of C12 diastereomers (10:1 dr)



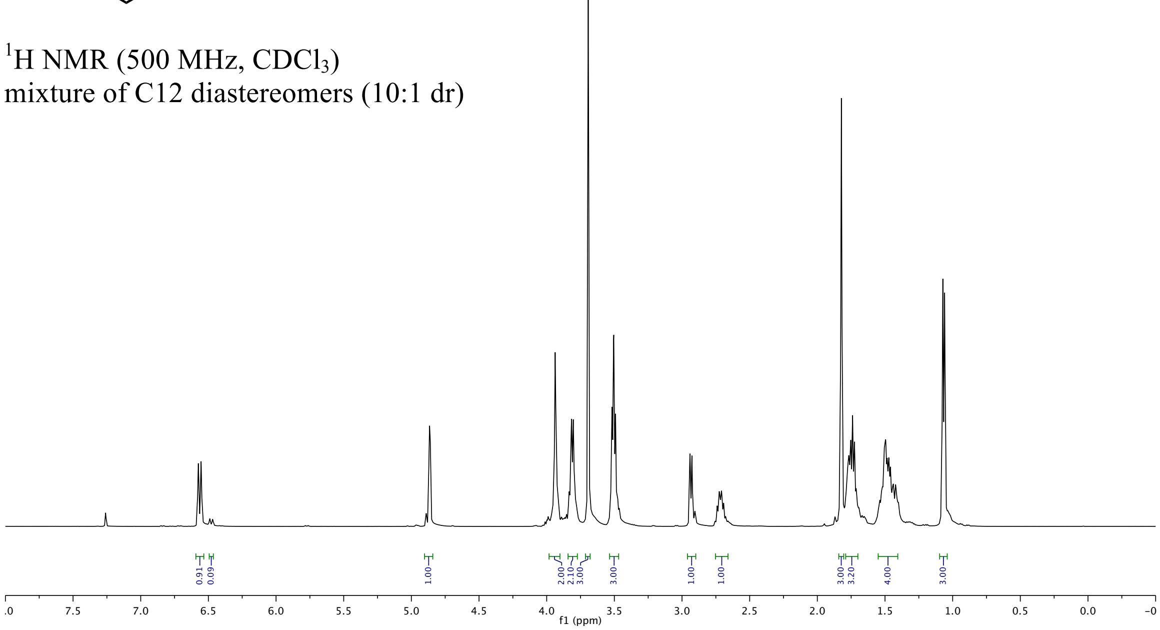
^{13}C NMR (125 MHz, CDCl$_3$)
mixture of C12 diastereomers (10:1 dr)



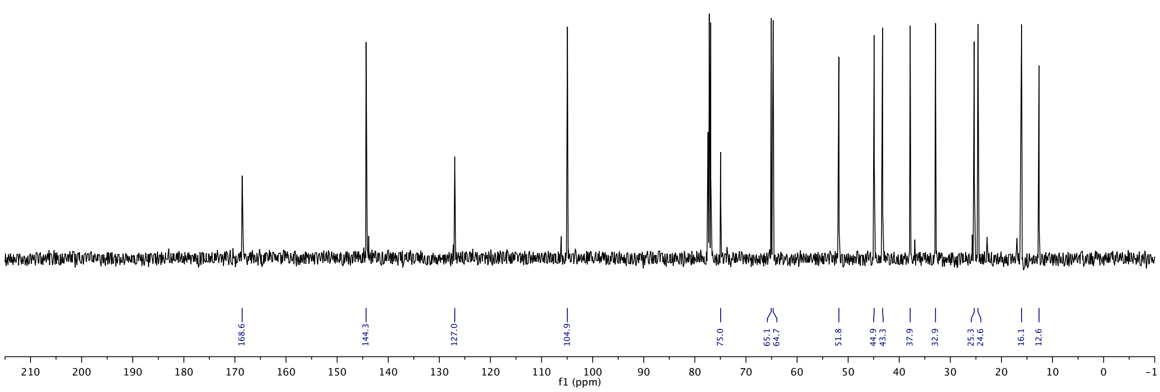


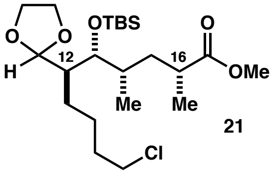
20

^{1}H NMR (500 MHz, $CDCl_3$)
mixture of C12 diastereomers (10:1 dr)



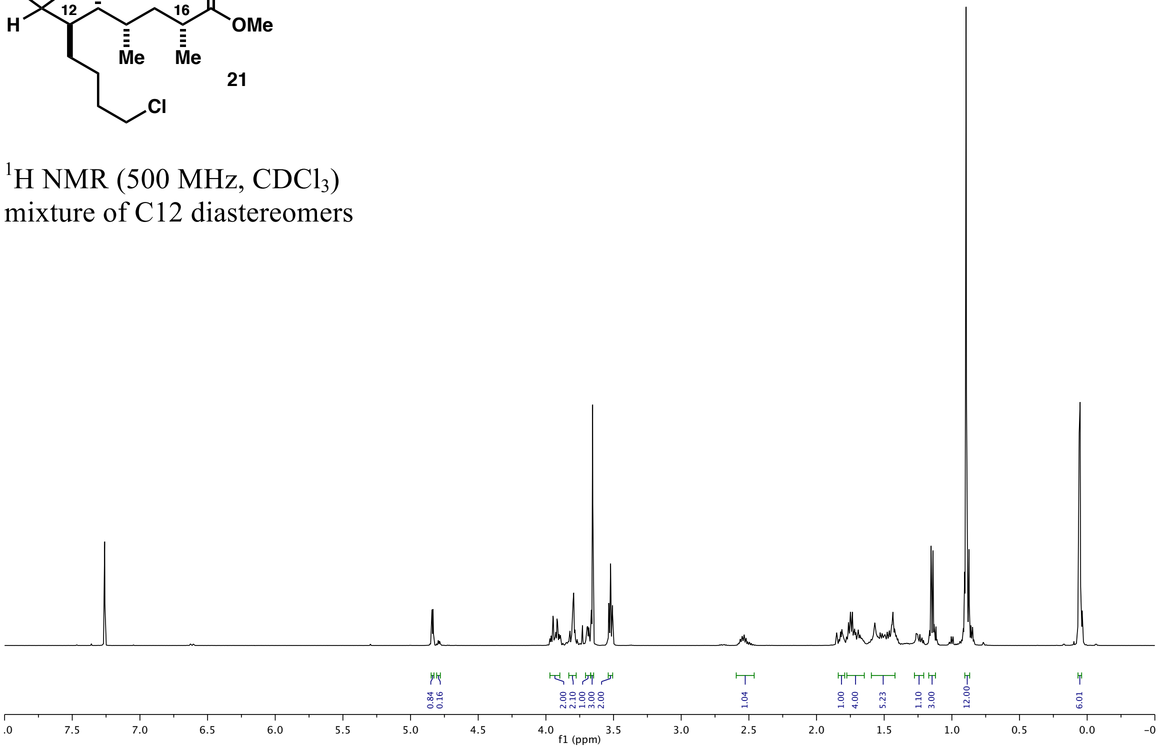
^{13}C NMR (125 MHz, $CDCl_3$)
mixture of C12 diastereomers (10:1 dr)



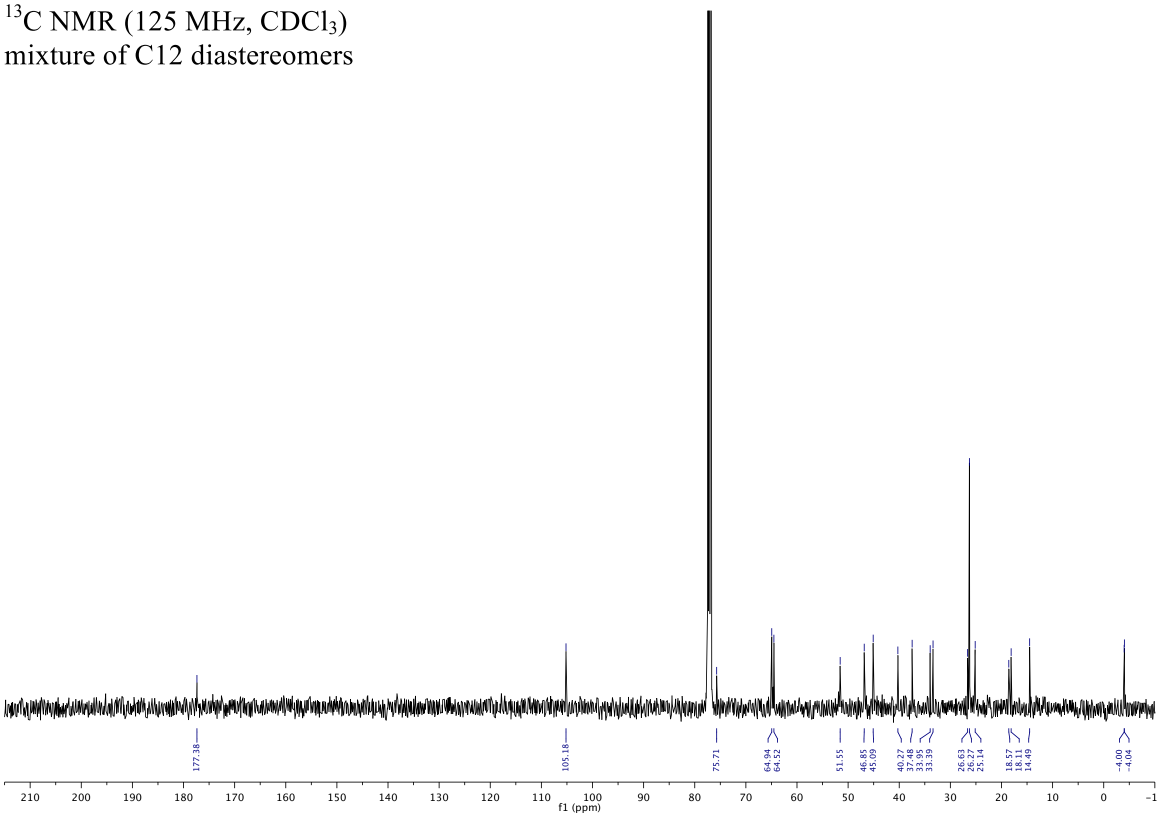


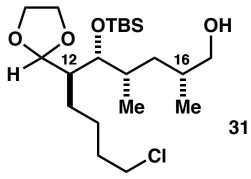
21

^{1}H NMR (500 MHz, CDCl$_3$)
mixture of C12 diastereomers



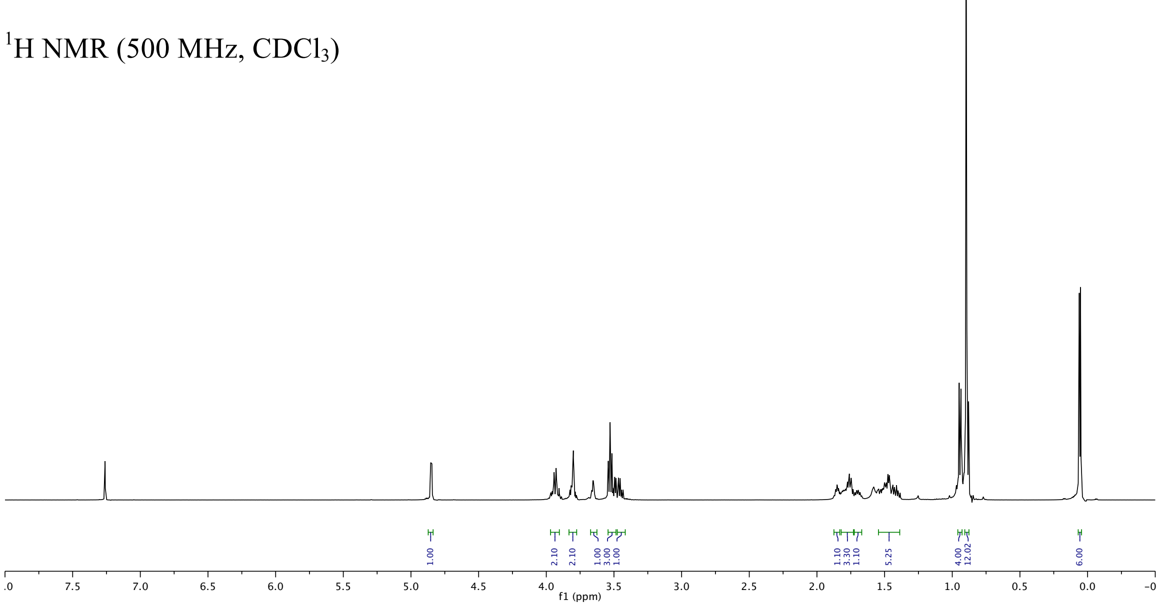
^{13}C NMR (125 MHz, CDCl$_3$)
mixture of C12 diastereomers



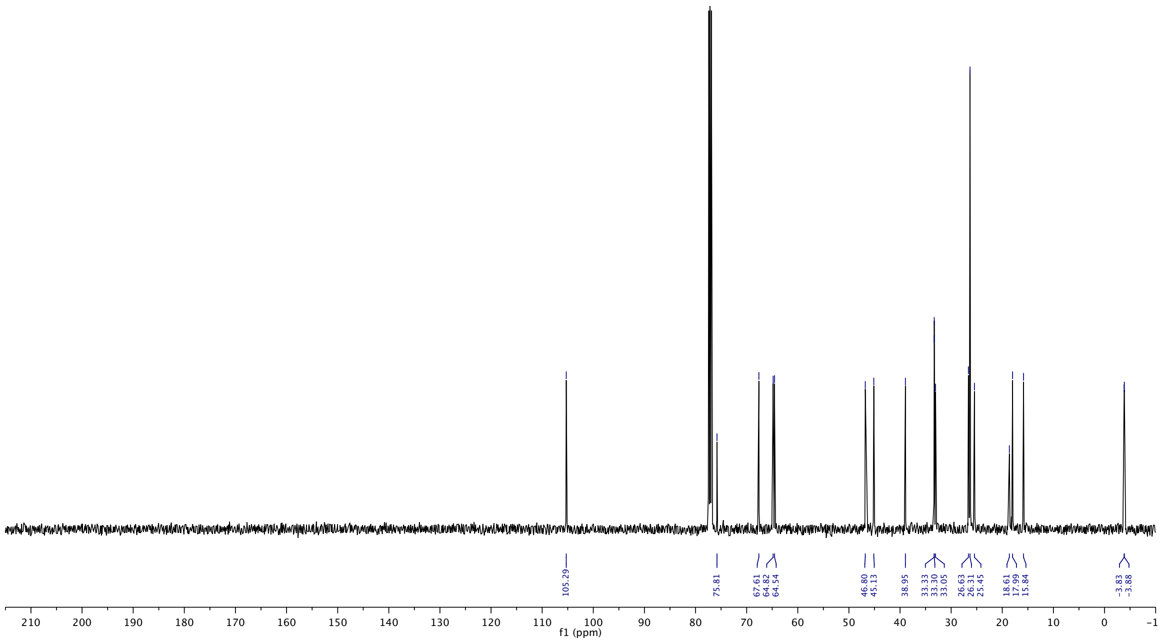


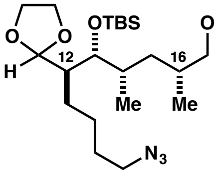
31

^{1}H NMR (500 MHz, CDCl$_3$)



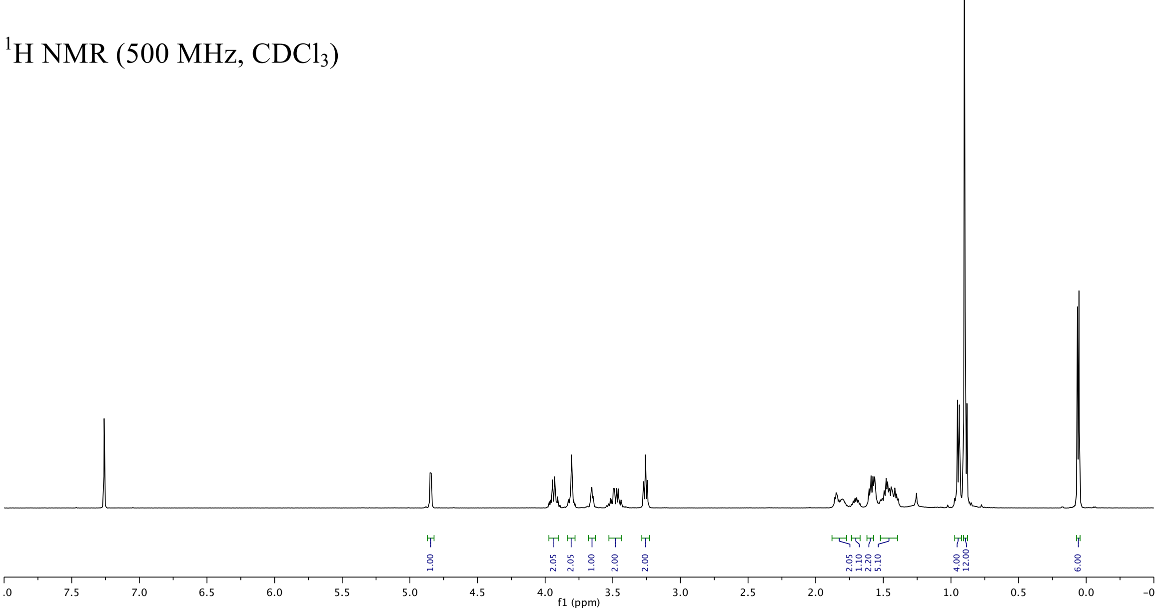
^{13}C NMR (125 MHz, CDCl$_3$)



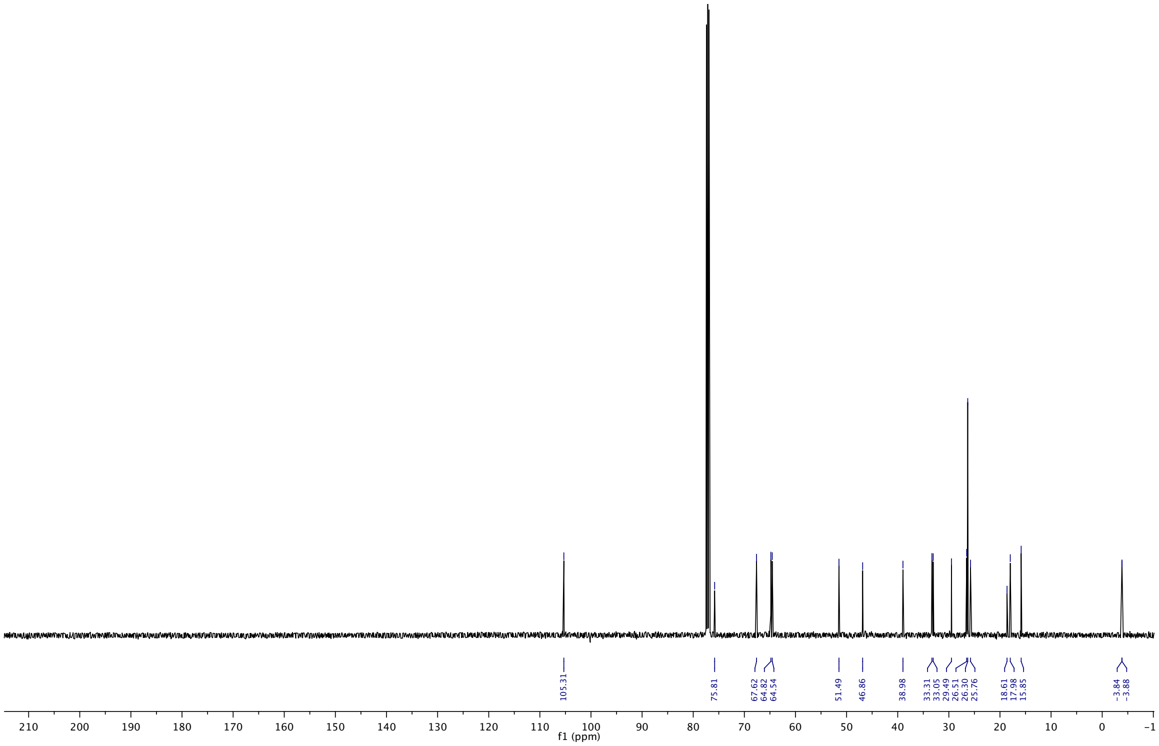


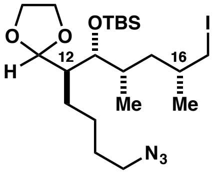
22

^{1}H NMR (500 MHz, CDCl$_3$)



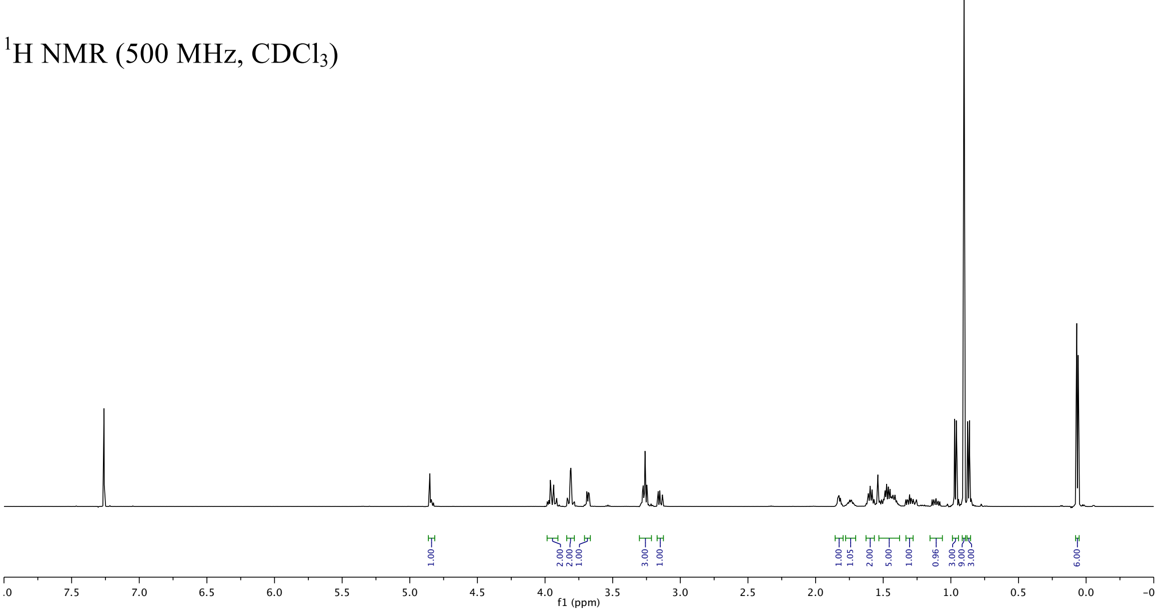
^{13}C NMR (125 MHz, CDCl$_3$)



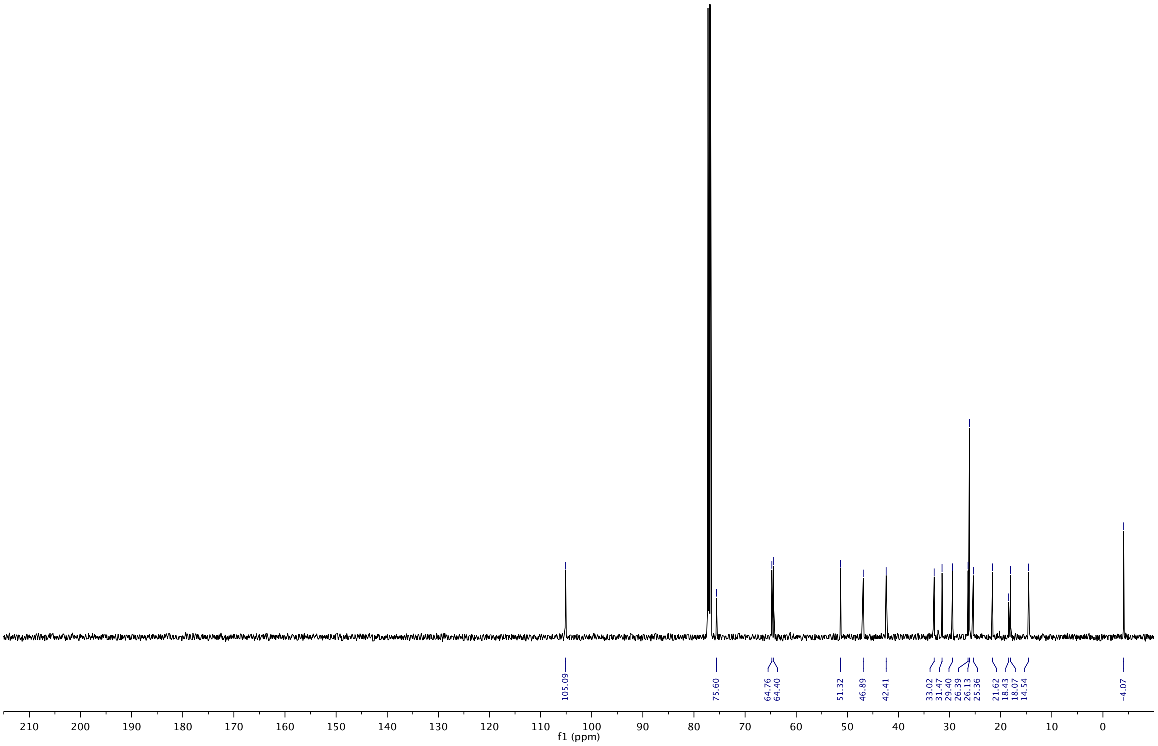


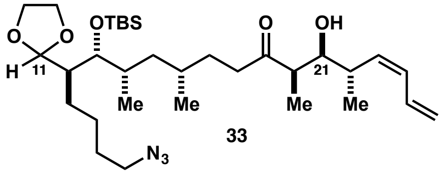
23

^{1}H NMR (500 MHz, CDCl$_3$)



^{13}C NMR (125 MHz, CDCl$_3$)





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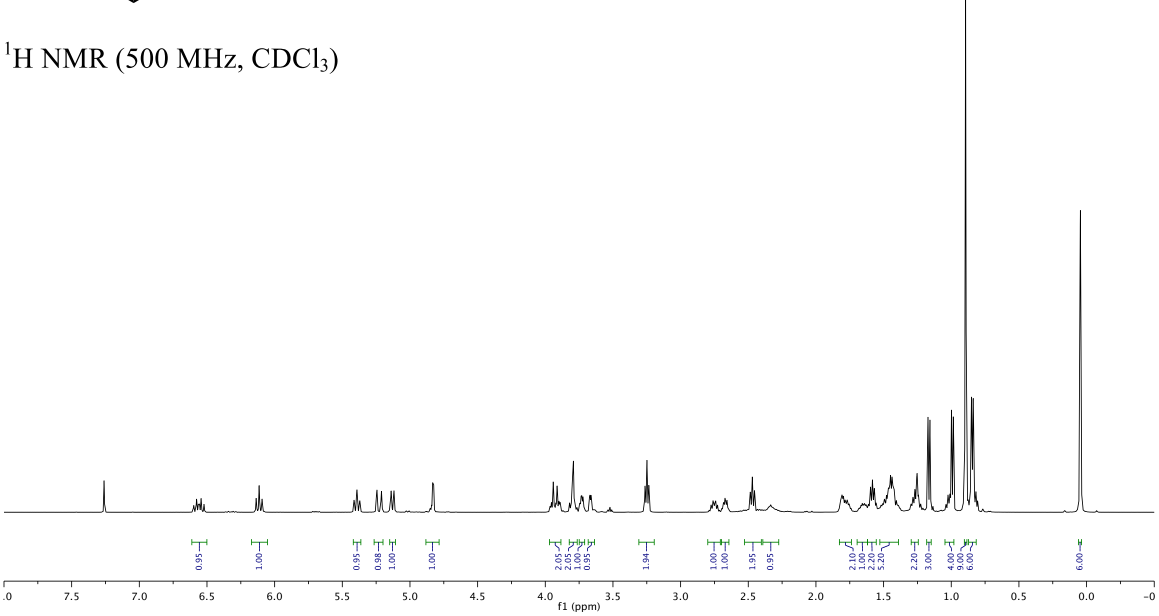
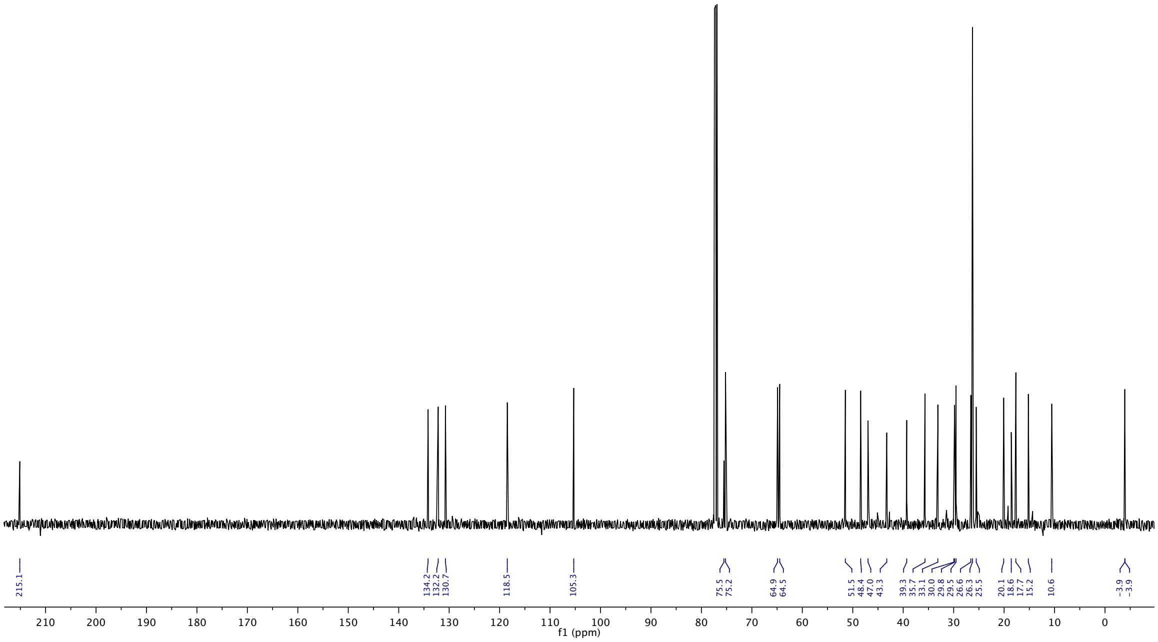
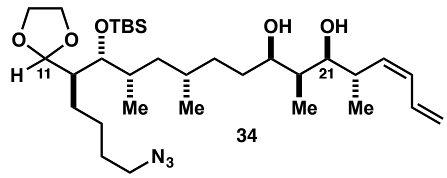


^{1}H NMR (500 MHz, CDCl$_3$)

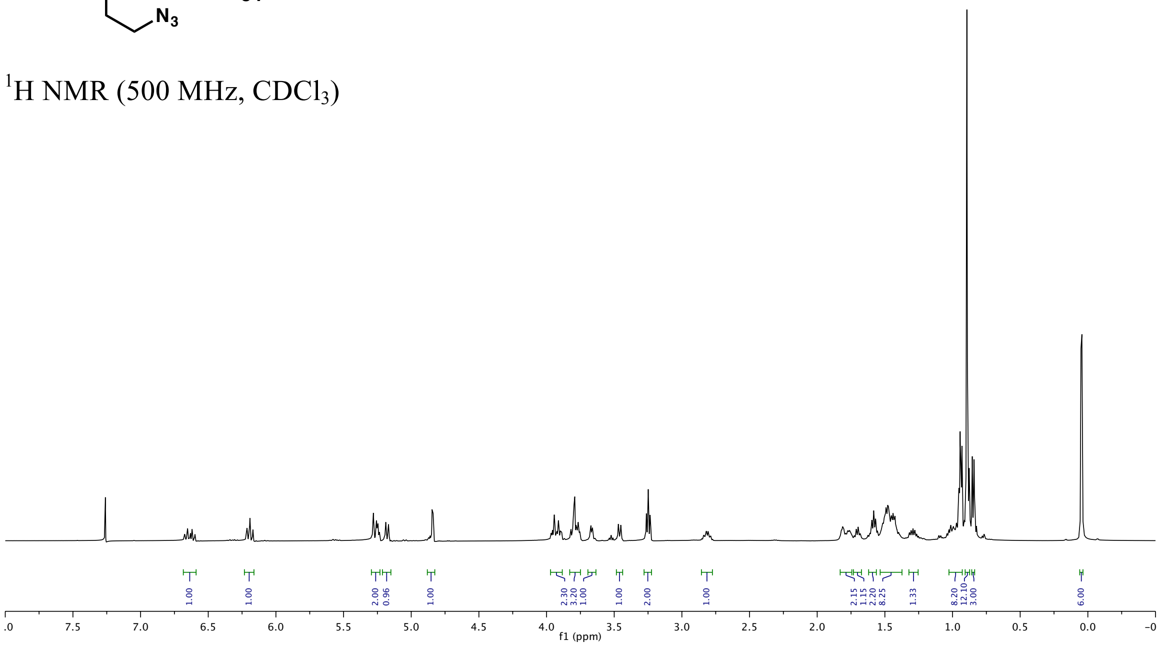
^{13}C NMR (125 MHz, CDCl$_3$)



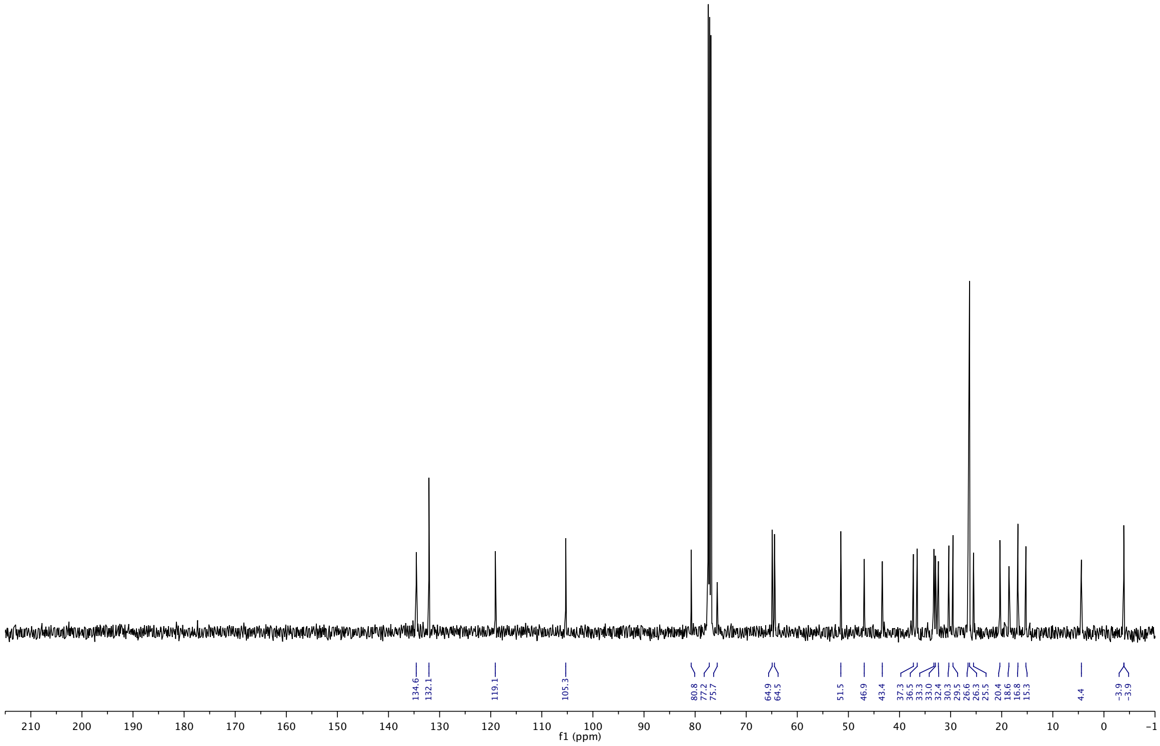


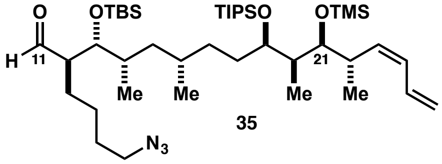
34

^{1}H NMR (500 MHz, $CDCl_3$)



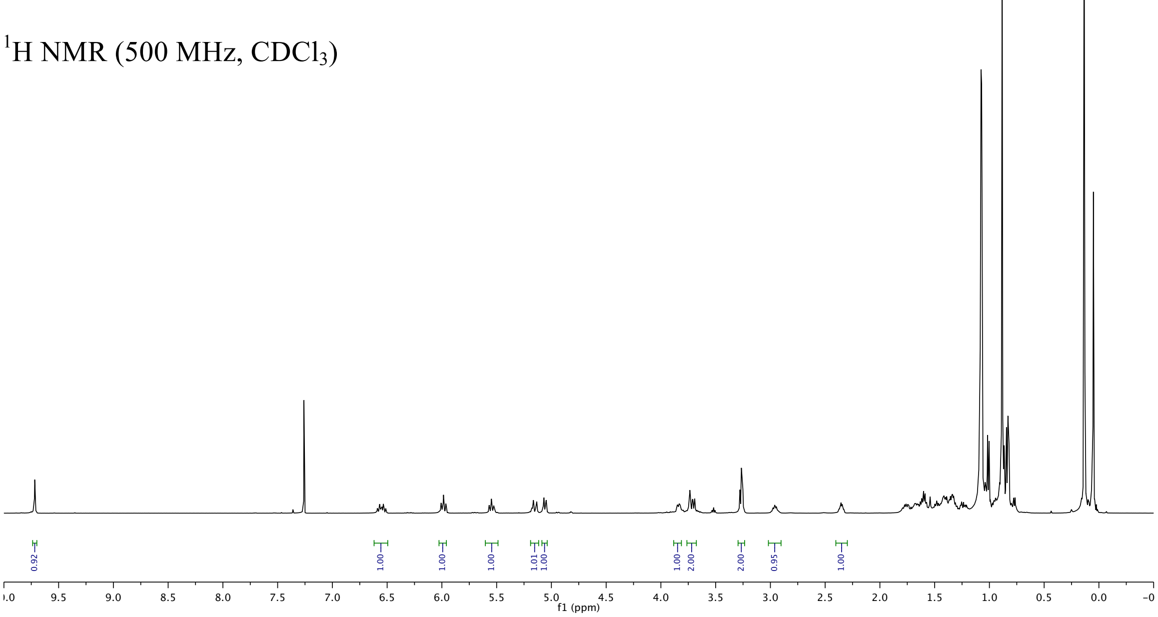
^{13}C NMR (125 MHz, $CDCl_3$)



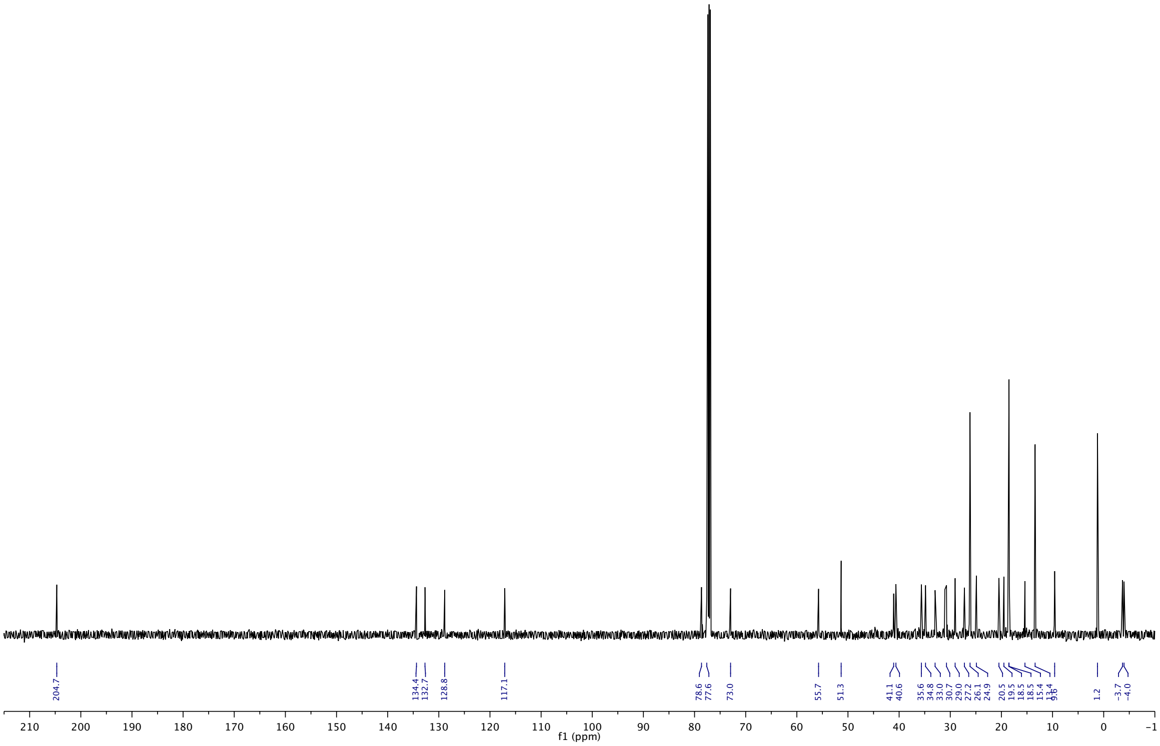


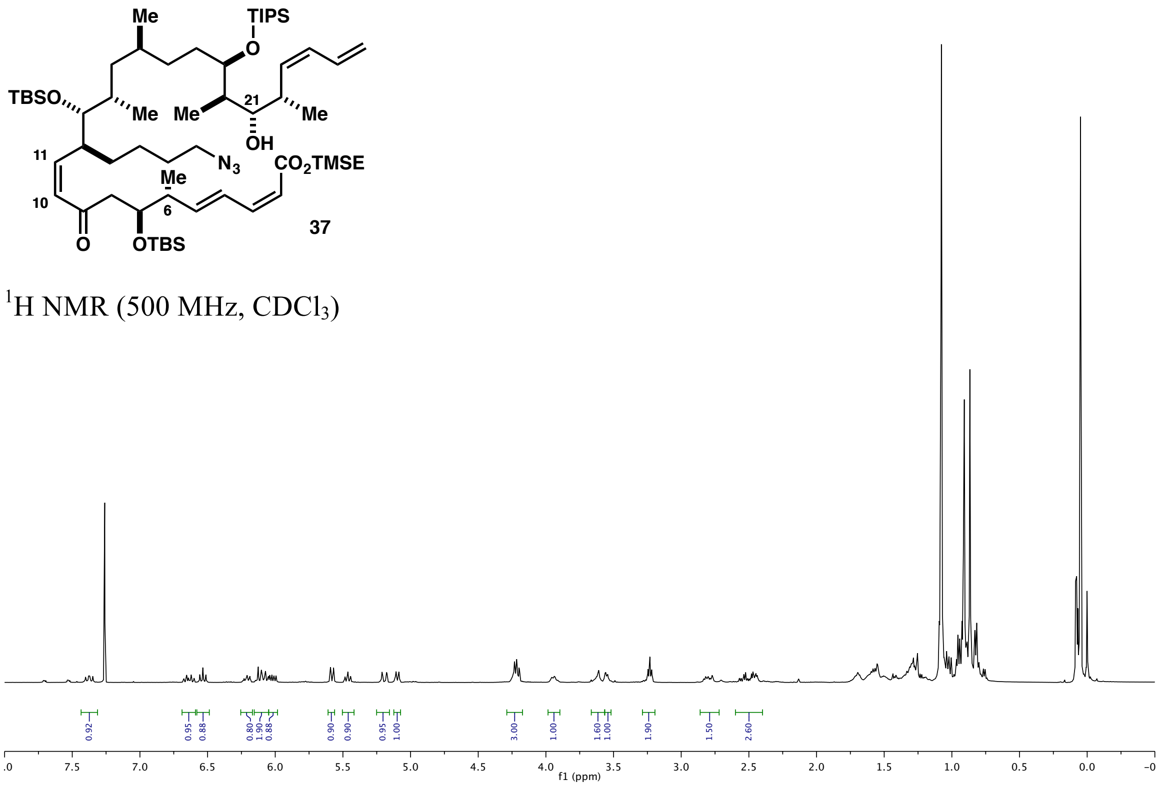
35

^{1}H NMR (500 MHz, CDCl$_3$)



^{13}C NMR (125 MHz, CDCl$_3$)

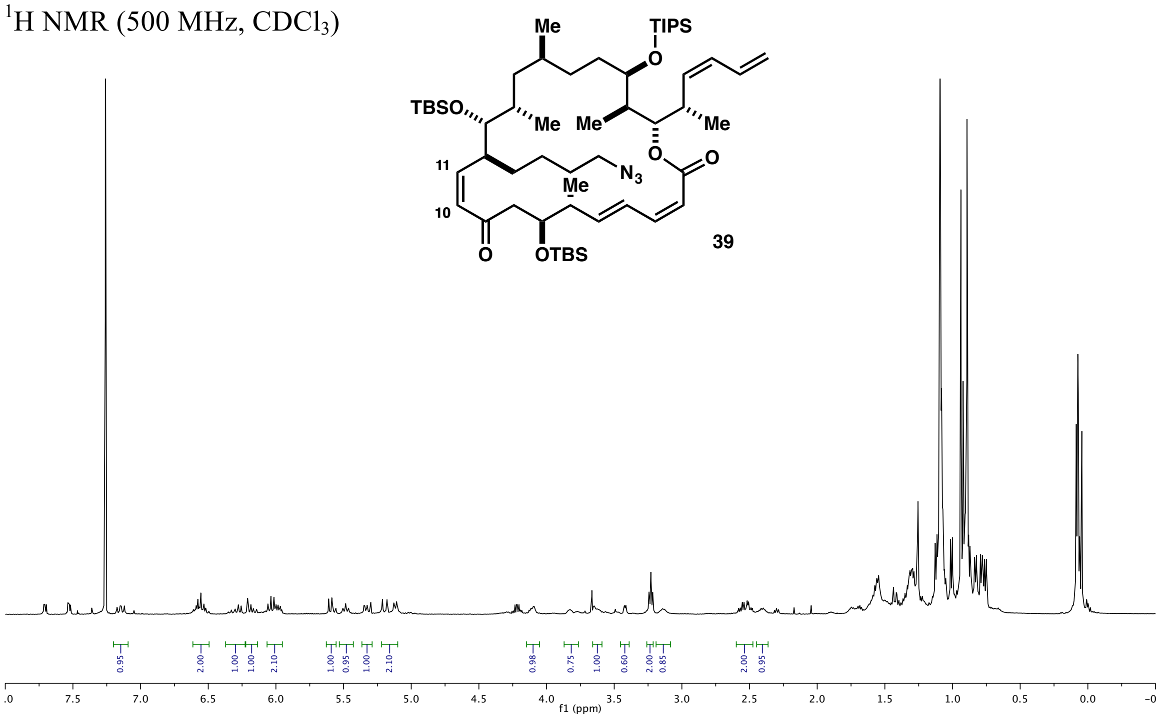




37

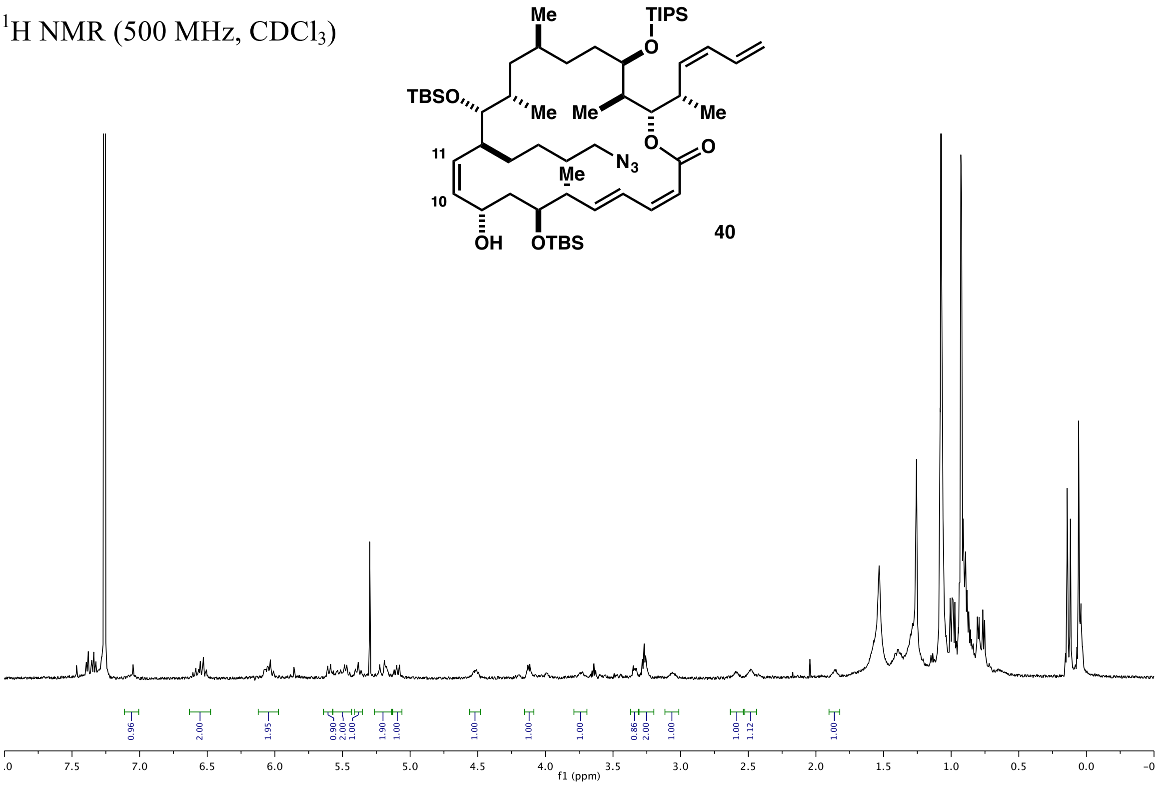
^{1}H NMR (500 MHz, CDCl$_3$)

^{1}H NMR (500 MHz, CDCl$_3$)

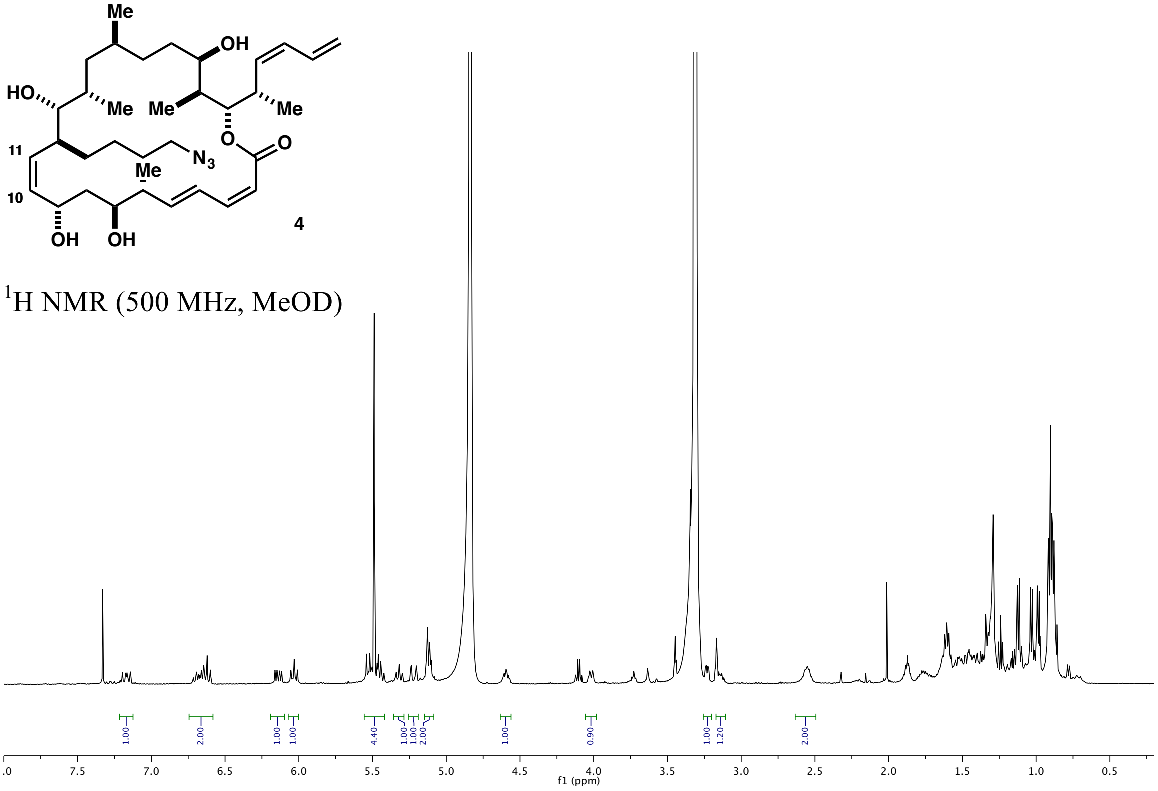


39

^{1}H NMR (500 MHz, CDCl$_3$)

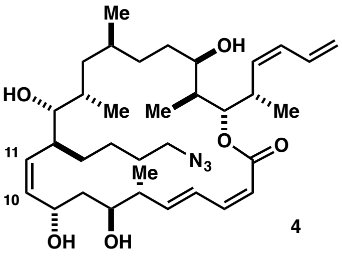


40



4

^{1}H NMR (500 MHz, MeOD)



4

COSY (500 MHz, MeOD)